EPA Response to Public Comments Related to the Supplemental Files Supporting the TSCA Scope Documents for the First Ten Risk Evaluations

May 2018

Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, DC

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This document provides the responses of the U.S. Environmental Protection Agency (EPA)/Office of Pollution Prevention and Toxics (OPPT) to the public comments on the supplemental files supporting the scope documents for the risk evaluations of the first ten chemicals that EPA is conducting under the amended Toxic Substances Control Act (TSCA). These supplemental documents discussed the initial systematic review activities for the TSCA risk evaluations, specifically the data gathering and literature screening strategy.

The *Strategy for Conducting Literature Searches* describes the initial methods, approaches and procedures that EPA used for identifying, compiling and screening publicly available information to support the development of the TSCA risk evaluations. The *Bibliography* documents for each TSCA scope document provide the bibliographic citations that were identified from the initial literature search and included based on the title and abstract screening.

EPA released the documents to the public on June 22, 2017. EPA opened the dockets on June 19, 2017 to receive information from the public. The public comment period ended on September 19, 2017.

Table 1 lists the chemical substances under evaluation, docket number information and web links where the *Strategy for Conducting Literature Searches* and *Bibliography* documents can be found along with the associated TSCA Scope documents and public comments. Table 2 summarizes the public comments that EPA received for the supplemental files.

Table 1. Docket and Web Link Information for the TSCA Scope Documents and Associated Supplemental Files

Chemical Name	CASRN	Docket Number	Web link to TSCA Scope, Literature Search Strategy and Bibliography Documents
Asbestos	1332-21-4	EPA-HQ-OPPT-2016-0736	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/asbestos-scope-document-and-supplemental-files"]
1-Bromopropane (1-BP)	106-94-5	EPA-HQ-OPPT-2016-0741	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/1-bromopropane-1-bp-scope-document-and-supplemental"]
Carbon Tetrachloride (CCl_4)	56-23-5	EPA-HQ-OPPT-2016-0733	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/carbon-tetrachloride-scope-document-and-supplemental"]
1,4-Dioxane	123-91-1	EPA-HQ-OPPT-2016-0723	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/14-dioxane-scope-

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			document-and-supplemental-files"]
Cyclic Aliphatic Bromide Cluster (HBCD)	25637-99-4; 3194-55-6; and 3194-57-8	EPA-HQ-OPPT-2016-0735	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/cyclic-aliphatic-bromides-cluster-hbcd-cluster-scope"]
Methylene Chloride	75-09-2	EPA-HQ-OPPT-2016-0742	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/methylene-chloride-scope-document-and-supplemental-files"]
N-Methylpyrolidone (NMP)	872-50-4	EPA-HQ-OPPT-2016-0743	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/n-methylpyrrolidone-nmp-scope-document-and-supplemental"]
Perchloroethylene (PERC)	127-18-4	EPA-HQ-OPPT-2016-0732	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/perchloroethylene-scope-document-and-supplemental-files"]
Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone; PV29)	81-33-4	EPA-HQ-OPPT-2016-0725	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/pigment-violet-29-anthra219-def6510-defdiisoquinoline"]
Trichloroethylene (TCE)	79-01-6	EPA-HQ-OPPT-2016-0737	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/trichloroethylene-tce-scope-document-and-supplemental"]

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Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	**Commenter**	**Comment Summary**	**EPA's Response**
1	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should consider other tools for systematic review: EPA has also proposed to extract data results in the DRAGON software. We strongly encourage EPA to also consider other potential software tools that have been developed and actively incorporated into the process of systematic review, such as Swift Reviewer, Active Screener, HAWC (Health Assessment Workplace Collaborative).	*Response for comments #1-3* EPA/OPPT is considering the use of various tools and/or approaches to support the various stages of the systematic review process of TSCA risk evaluations. DRAGON and DistillerSR are examples of tools that EPA/OPPT uses for the systematic review of TSCA risk
2	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should incorporate appropriate tools for updating and evaluating systematic reviews in their chemical assessments. EPA should evaluate the Cochrane Collaboration panel's tool for updating guidance for systematic reviews, published guidance in 2016 for determining when it is appropriate to update a systematic review and outlining the steps for performing the update to assess the applicability of environmental chemicals given that Cochrane systematic reviews. It will be critical for EPA to develop tools to assist with the process of evaluating existing systematic reviews, particularly as this field continues to rapidly expand and more systematic reviews relevant to environmental health questions are published in the scientific literature, potentially of variable quality. One tool which might be helpful for evaluating the risk of bias in systematic reviews is the ROBIS tool, which the NAS committee utilized in their report. Another tool which may be helpful in this process is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), used by authors of systematic reviews to improve the reporting of elements relevant to the systematic review and meta-analyses. We also strongly recommend EPA identify tools that may potentially not be appropriate for human health chemical assessments without modification, such as those developed in other fields, such as clinical or preclinical animal or human studies.	
3	[HYPERLINK	TCE Section 5.3.1, p.15: While EPA has limited its data to that which is publically	

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	"https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	available, it appears that the software being used by those who will screen the data is proprietary, i.e., IFC's DRAGON. It is not clear whether the public will be able to access this database and/or see how the software instructs, encourages, or limits the options for the reviewer. We suggest that EPA provide snap-shots of pages used by the reviewers, as well as the results of the analyses.	evaluations. EPA/OPPT is considering the adoption of the OECD Harmonized Templates (OHTs) for extracting various data streams. EPA/OPPT is exploring to use DistillerSR as the tool for data extraction. EPA/OPPT will rely on HERO as the "warehouse" for all citations included in the TSCA risk

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			evaluations. Each chemical assessment has a "project page" that will be made public when EPA publishes the draft risk evaluations. EPA/OPPT is committed to transparency and will provide documentation of how the systematic review has been conducted to support the TSCA

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			risk evaluations.
4	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0735-0058"]	We request that EPA provide (1) a clear definition of "off topic" and "on-topic" and (2) a general scope of how "off topic" and "on-topic" studies are anticipated to be utilized in the evaluation. For example, are "off topic" studies only identified and utilized as supporting information to confirm [or reject] information found in "on-topic" studies?	EPA/OPPT included definitions of on-topic and off-topic references on page 2 of each *Bibliography* document that accompanied each TSCA Scope document. Also the definition was included in section 1.3 of each TSCA Scope document. The definitions have also been

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#	**Commenter**	**Comment Summary**	**EPA's Response**
			included in section 3.2.2.1.1 of document entitled *Application of Systematic Review in TSCA Risk Evaluations*.
5	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should provide exclusion reasons for off topic citations.	*Response for comments #5-6*
6	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should stratify its exclusion criteria separately at the title and abstract and full text screening steps.	The *Strategy for Conducting Literature Searches* documents provided the inclusion

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			and exclusion criteria used for the title/abstract screening. References that did not meet the inclusion criteria were excluded and considered *off-topic*. The inclusion and exclusion criteria for full text screening are included in each of the TSCA Problem Formulation documents for the first

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			ten chemical assessments .
7	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should not exclude studies based on language.	EPA/OPPT will translate studies on a case-by - case basis.
8	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should have two independent reviewers for screening steps.	*Response for comments #8-11* EPA/OPPT pilots the screening criteria to ensure a level of proficiency of each screener in each subject matter area. Additionally, each article is generally screened by two different
9	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should clearly document decisions related to the identification and search. Particularly, the number of studies that are reviewed by a senior-level technician and the feedback and guidance provided to individual screeners.	
10	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should clarify how it will handle discrepancies in the inclusion/exclusion and tagging process and use a third party reviewer as an arbiter for decisions when consensus is not reached.	
11	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should clearly outline the process for handling anticipated overlap with literature relevant to multiple topics. EPA should describe whether the same reviewer will be responsible for screening papers with inclusion/exclusion criteria across multiple topics or whether different reviewers are responsible only for screening studies for one particular topic.	

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			reviewers. All of the screening decisions are being documented. Refer to the *Strategy for Conducting Literature Searches* documents and section 3.2.2.1 of document entitled *Application of Systematic Review in TSCA Risk Evaluations* for more information on the title/abstract screening

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12	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should explicitly include stopping rules in the form of deadlines or criteria for when the body of included relevant studies will be finalized for the purposes of the chemicals assessment.	The body of information compiled in the *Bibliography* documents for each TSCA scope document will be the primary pool of studies that will be considered in the TSCA risk evaluations along information submitted during public comment periods prior to the publication of the draft TSCA risk evaluations.

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			Targeted supplemental searches may be conducted to address specific needs for the analysis phase (e.g., to located specific data for building exposure scenarios and modeling).
13	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should ensure gray literature search results are adequately screened. EPA's gray literature search strategy proposes to utilize Google's API to develop custom searches and return the first 100 results, sorted by predicted relevancy so that the results likely to be most relevant are screened first. We recommend that EPA ensure that an adequate number of search results are screened. EPA should consider "snowball searching," where the citations of included (i.e., on-topic) references are searched as well as using databases such as Web of Science to search for references that cite the included citations.	EPA/OPPT will include backward searching (also called snowball searching) in future searches. EPA/OPPT may refine

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			the search strategy for future assessments to ensure that relevant gray literature is captured.
14	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	TCE Section 4.4, p.14: With regard to the exclusion criterion, "Links that were broken at the time of the search", an additional search step may find them before exclusion. We suggest that a search engine such as Google be used to see if title of the document is sufficient to obtain a working URL.	Two types of broken links were identified when searching for gray literature: (1) those associated with entire sites that were "down" or inactive and (2) links on active sites that were no longer

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			appropriate. In the event of the latter, particularly for links on EPA's website, which has recently undergone a large-scale reorganization, the title of documents will be searched via Google to determine if the document is available at another location.
15	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	TCE Section 4.4, p.14: In the exclusion criterion for peer-reviewed articles, "peer reviewed literature was assumed to be captured in searches of the databases of peer-reviewed literature." If the databases of peer-reviewed literature are based on journals, books, and government reports, the conclusion in the criterion may not be valid. For TCE for example, Toxicology Excellence for Risk Assessment	Peer reviewed literature that was captured

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		(TERA, now part of the University of Cincinnati) had an externally peer reviewed analysis of EPA's RfC that was publically available months before it was published in a journal. This may also be true for many analyses and reviews performed in State regulatory agencies that, unlike academia, do not include journal publications in their criteria for professional advancement.	during the search of the gray literature was excluded only if it was clearly shown to be available in the peer-reviewed literature, for example, with a journal citation and/or DOI. The peer reviewed analysis by TERA referenced in the comment would not be excluded from the results of

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			the gray literature search. The TERA reference will be added to the on-topic pool of references supporting the TSCA risk evaluation for trichloroethylene.
16	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should rely on existing IRIS assessments for hazard identification. Moving forward, EPA should complete hazard identification or add additional studies only through a systematic review process, which integrates animal, human and mechanistic evidence as recommended by the recent NAS report. For the scoping document, EPA should include all hazards identified in the literature, and not make decisions about their relevance to the risk evaluation until a systematic review has been completed. EPA should develop criteria to evaluate the internal validity (risk of bias) of individual studies, utilizing existing tools that have been developed and empirically demonstrated on environmental health studies such as the Navigation	*Response for comments #16-18* EPA/OPPT will use previous assessments such as the IRIS assessments

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		Guide or the Office of Health Assessment and Translation (OHAT approach). We also recommend that EPA not using a scoring system to evaluate study quality. Data generated by alternative test methods (such as high-throughput screening methods) are not different than any other type of in vitro or cell-based assay data that would be considered in a systematic review. These data can be used to support conclusions, but hazard classification should never be made based on high-throughput or other kinds of mechanistic data alone.	as a starting point for identifying key and supporting studies to inform the human health hazard assessment, including dose-response analysis. The relevant studies will be evaluated using the data/information quality criteria in the document entitled *Application of Systematic*
17	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0061"]	Use of existing IRIS assessments: To assist the Agency in meetings its deadlines for risk evaluations, previous findings on hazard and risk from the IRIS assessments should be presumed valid and incorporated in risk evaluations. Moving forward, EPA should complete hazard identification or add additional studies through a systematic review process, which integrates animal, human and mechanistic evidence as recommended by the recent NAS report on Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Disrupting Chemicals [ADDIN EN.CITE <EndNote><Cite><Author>National Academy of Sciences</Author><Year>2017</Year><RecNum>35</RecNum><IDText>3982546</IDText><DisplayText>(National Academy of Sciences, 2017)</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="wfedfw0vlx9tdjedfrmpp5e52sfrwe555ptt" timestamp="1511286716">35</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>National Academy of Sciences,</author></authors></contributors><titles><title>Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active	

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		chemicals</title></titles><pages>180</pages><dates><year>2017</year></dates><pub-location>Washington, D.C.</pub-location><publisher>The National Academies Press</publisher><label>3982546</label><urls><related-urls><url>http://dx.doi.org/10.17226/24758</url></related-urls></urls><electronic-resource-num>10.17226/24758</electronic-resource-num><language>English</language></record></Cite></EndNote>].	*Review in TSCA Risk Evaluations.* Refer to each of the TSCA Problem Formulation documents for details on how the PECOs are considering the information of the IRIS assessments for setting inclusion criteria for the full text screening. Regarding negative studies, the weight of evidence analysis is
18	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	TCE Section 3.3.1, p.9-10: The intent appears to be to use the IRIS 2011 evaluation without independent review of the literature, and to start the literature search at January 2010. However, [HYPERLINK "file:///C:\\Users\\Iris%20Camacho\\Desktop\\TSCA%20SR%20protocol_v9_121617_clean_beck_template.docx" \l "_ENREF_27" \o "U.S. EPA, 2011 #65"] discounts the negative rat studies as "not entirely adequate", even including the NTP 1988 study which was designed to overcome the high mortality in the NCI 1976 and NTP 1990 rat studies that had high mortality (using the same rat strain) by using five different strains of rat. While one was the same as the two previous, presumably as a control, that was not the case for all of the rat strains. Similarly, [HYPERLINK "file:///C:\\Users\\Iris%20Camacho\\Desktop\\TSCA%20SR%20protocol_v9_121617_clean_beck_template.docx" \l "_ENREF_27" \o "U.S. EPA, 2011 #65"] states "Weaknesses in the evidence include lack of a clear dose-related response in the incidence of cardiac defects, and the broad variety of cardiac defects observed, such that they cannot all be grouped easily by type or reported inhalation studies being negative for developmental toxicity, EPA's document uses the positive results in oral studies to calculate the RfC. We suggest that, at a minimum, TSCA independently review the data in the negative studies discounted by the IRIS document, as well as any recent publication. These example cited in the full comment demonstrate the discounting credible negative results in favor of positive studies regardless of route of exposure. Use of PBPK modeling is not justified for route-of-exposure extrapolation when data exist for that route of exposure.	

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			an integrative and interpretive process that considers both data/information in favor (e.g., positive study) or against (e.g., negative study) a given hypothesis within the context of the assessment question(s) being evaluated in the risk evaluation.

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Abbreviations in Table 2	
ACC NAFRA=American Chemistry Council North American Flame Retardant Alliance	NTP=National Toxicology Program
API=Application Programming Interface	OHAT=The NTP Office of Health Assessment and Translation
DOD=United States Department of Defense	OECD=Organisation for Economic Co-operation and Development
DOI=Digital Object Identifier	OPPT=The Environmental Protection Agency Office of Pollution Prevention and Toxics
DRAGON=	PBPK=Physiologically-based pharmacokinetic
EPA=Environmental Protection Agency	PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses
EPA/OPPT=Environmental Protection Agency Office of Pollution Prevention and Toxics	ROBIS=tool for assessing Risk of Bias in systematic reviews
HERO=Health and Environmental Research Online	TERA=Toxicology Excellence for Risk Assessment
IRIS=Integrated Risk Information System	TCE=Trichloroethylene
NAS=National Academy of Sciences	TSCA=Toxic Substances Control Act
NRDC=National Resources Defense Council	

EPA's RISK EVALUATION PROCESS and NEW CHEMICALS PROGRAM

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February 28, 2018
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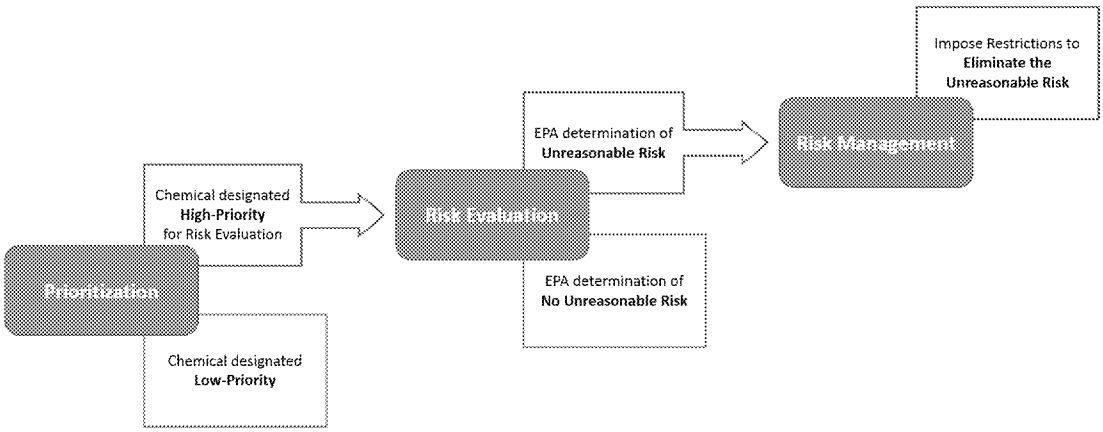
Overview

- Risk Evaluation
  - Statutory Requirements
  - 10 high priority chemicals
  - PBTs
- EPA's New Chemicals Program
  - Amended TSCA Determinations
  - Decision Framework
  - Implementation Tools

Evaluating Risks of Existing Chemicals



Risk Evaluation
Statutory Requirements

- EPA must establish by rule a process for risk evaluation; signed by Administrator in June 2017
  - Determine if a chemical presents an unreasonable risk of injury to health or the environment under conditions of use (i.e., the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, use, or disposed of)
  - Without consideration of cost or other non-risk factors
  - Including unreasonable risk to potentially exposed or susceptible subpopulation(s) determined to be relevant to the evaluation
- This process must be completed within 3 – 3.5 years
- For each risk evaluation completed, EPA must designate a new high-priority chemical
- By December of 2019, EPA must have initiated 20 high-priority chemicals for risk evaluation
  - Additional risk evaluations may come from manufacturer requests

Risk Evaluation
Statutory Requirements

- **First 10** Chemicals – Announced December 19, 2016

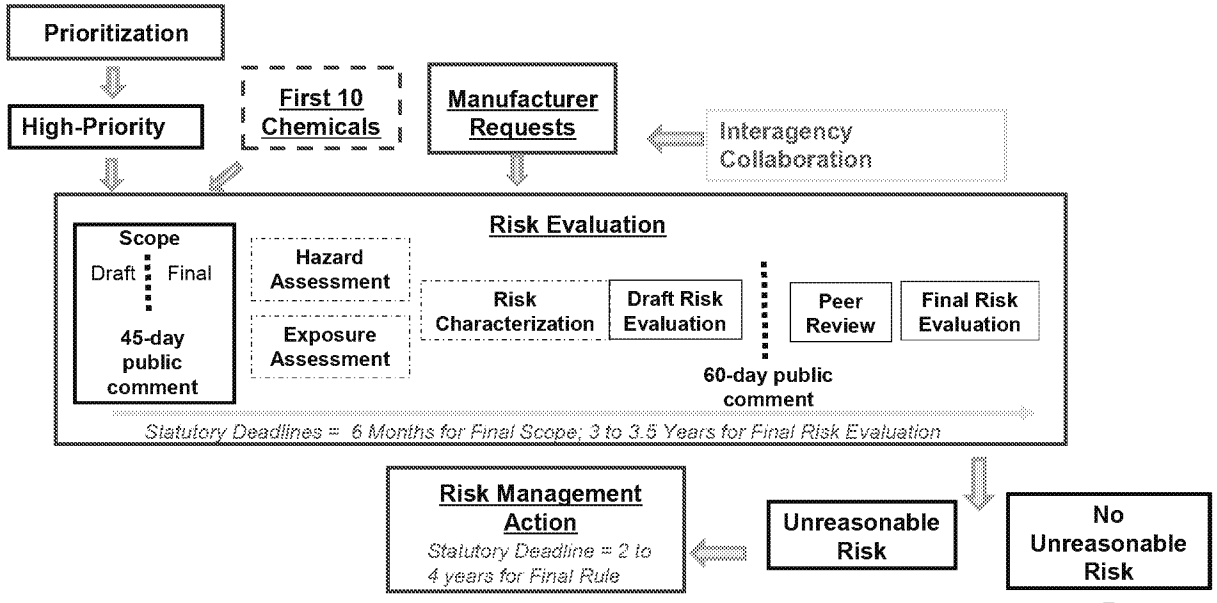
1, 4 Dioxane	Methylene Chloride
1-Bromopropane	N-Methylpyrolidone
Asbestos	Pigment Violet 29
Carbon Tetrachloride	Trichloroethylene
Cyclic Aliphatic Bromide Cluster (HBCD)	Tetrachloroethylene

- **Scope** – Publish within 6 months of initiation; must identify hazards, exposure, conditions of use, potentially exposed or susceptible subpopulation(s) EPA expects to consider
  - Scope documents published June 22, 2017
- **Problem Formulation** documents expected spring 2018

Risk Evaluation
Statutory Requirements

- **Draft Risk Evaluation**
  - Hazard Assessment – identification of types of hazards to human health and/or the environment
  - Exposure Assessment – the duration, intensity, frequency, and number of exposures under the conditions of use
  - Risk Characterization – integration of hazards and exposure into estimates of risk
  - Determination of Unreasonable Risk – does or does not present an unreasonable risk
  - Peer review – all evaluations will be peer reviewed
  - Publication and 30 day public comment period

Risk Evaluation Process and Timeline



Persistent, Bioaccumulative and Toxic Chemicals

- Statute requires a fast-track process for certain PBT chemicals on the TSCA Work Plan and for which exposure is likely based on a use and exposure assessment, unless a manufacturer requested a risk evaluation by Sep 19, 2016
  - Rulemaking is under development for 5 chemicals ~~are getting expedited action~~
  - Manufacturer requests received for 2 PBT chemicals
- No~~Use and exposure assessment required; no~~ formal risk evaluation
- Rules to address risks of injury to health or the environment and to reduce exposure~~,~~ to the extent practicable, must be proposed by June 2019 and finalized 18 months later
- ~~Additional requirements encourage consideration of o~~Other PBTs are to be addressed in overall risk evaluation process

New Chemicals Background

- 2016 Amendments to TSCA
  - Required EPA to make affirmative finding on new chemicals and significant new uses of existing chemicals, before they can enter the market
  - Effective immediately
  - New chemicals determinations made using risk-based approach, considering hazard and exposure, based on conditions of use
- Conditions of use
  - Means the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, use, or disposed of.

New Chemicals

Presents an unreasonable risk

- Section 5(f) order
- Section 6(a) proposed rule
- Restriction/prohibition of manufacturing, processing, distribution, or disposal

Not likely to present an unreasonable risk

- Commercialization can commence after the determination is made
- Section 5(g) – Statement in the FR

Information is insufficient to permit a reasoned evaluation of the risk

- Section 5(e) – Regulation pending more information
- Section 5(e) order
- Testing generally required

Insufficient information to permit a reasoned evaluation **and may present** unreasonable risk

- Section 5(e) – Regulation pending more information
- Section 5(e) order
- Testing generally required

Decision Framework

- "New Chemicals Framework" released for public comment at December 2017 public meeting; describes EPA's current working approach to make decisions on new chemical notices
- Intended conditions of use:
  - In general, these are the ~~The~~ circumstances around manufacture, processing, distribution in commerce, use, or disposal as stated in the submission (original or amended).
  - ~~If conditions of use identified in submissions raise risk concerns, submitters may provide timely written amendments to their submissions addressing those concerns.~~
  - In general, EPA will consider the amended conditions of use to be the intended conditions of use.

Decision Framework

- Reasonably foreseen conditions of use:
  - Identification of any reasonably foreseen conditions of use will be fact- or knowledge-specific; based on evidence, knowledge, or experience leading EPA to foresee conditions of use different from those described in the submission.
  - ~~If EPA has concerns with intended *and* reasonably foreseen conditions of use, EPA will generally issue orders followed by significant new use rule (SNURs)~~
  - ~~If EPA has concerns with reasonably foreseen conditions of use, but *not* with the intended conditions of use, EPA will assess whether those concerns can be addressed through SNURs *without* orders~~

~~Decision Framework~~

~~Non-order SNUR:~~

- ~~Considered when EPA has concerns with certain reasonably foreseen conditions of use, but not with the intended conditions of use as described in a submission (original or amended)~~
- ~~Under When this approach is used, EPA could would make a "not likely to present unreasonable risk" finding for the PMN uses, and use a SNUR to require a Significant New Use Notification (SNUN) for the "reasonably foreseen" uses~~
- ~~EPA would evaluate any SNUNs submitted to determine how best to address risk for those reasonably foreseen conditions of uses~~

Pre-Submission Support

- Two common issues with ~~problems in~~ submissions
  - Information does not allow for refinement of risk assessment
  - Submitter has useful information (e.g., analog data) but it's not provided to EPA
- New *draft* Points to Consider document
  - Issued in November 2017
  - Will provide ~~Provides~~ concise guidance to strengthen ~~improve~~ PMN submissions – largely based on existing documentation
  - Will promote more robust ~~Promotes better~~ submissions, supported by robust pre-submission consultation "program"

Pre-Submission Support

- Pre-consultation meetings
  - Understanding of information useful to EPA's review
  - Helps improve submission quality and program efficiency
- Sustainable Futures Program
  - Provides companies with risk-screening models and training to help develop safer chemicals quickly and cost-effectively.
  - Participating companies become eligible for an expedited EPA pre-manufacture review
  - Contains description of most of the risk assessment process including models and tools
  - Gives insights on what types of engineering processes and releases will be calculated

Pre-Submission Support

- New Chemicals Decision Guidelines Manual
  - Under development
  - Draft outline shared at December 2017 public meeting
  - Will provide submitters with information on how EPA conducts its new chemicals assessments
  - Will help stakeholders determine what forms of regulation and restrictions might be imposed on the manufacture, processing, distribution, use, and/or disposal of a new chemical substance
- Chemical category documents

Next Steps

- Considering public comments from December 2017 public meeting and on documents released in connection with the meeting
  - ~~Developing new Questions and Answers for website~~
- Continuing to develop and revise as appropriate the Decision Framework to accurately reflect OPPT's working approach as it evolves
  - Considering comments received
- Utilizing Points to Consider document and encouraging pre-submission consultation
  - Considering comments received
- Improving data systems to enhance ability to track, search and manage new chemical reviews
- Identifying opportunities to streamline processing
- Promoting transparency
- Continuing to improve overall performance

For More Information

https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/frank-r-lautenberg-chemical-safety-21st-century-act

Contact EPA at

https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/forms/assessing-and-managing-chemicals-under-tsca

EPA's NEW CHEMICALS PROGRAM and RISK EVALUATION PROCESS

Tanya Hodge Mottley
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
February 28, 2018
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Overview

- EPA's New Chemicals Program
  - Amended TSCA Determinations
  - Decision Framework
  - Implementation Tools
- Risk Evaluation
  - Statutory Requirements
  - 10 high priority chemicals
  - PBTs

Background

- 2016 Amendments to TSCA
  - Required EPA to make affirmative finding on new chemicals or significant new uses of existing chemicals, before those chemicals can enter the market
  - Effective immediately; 90 day review process, with EPA ability to extend another 90 days
  - New chemicals determinations made using risk-based approach, considering hazard and exposure, based on conditions of use
- Conditions of use
  - Means the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, use, or disposed of.

New Chemicals

Presents an unreasonable risk

- Section 5(f) order
- Section 6(a) proposed rule
- Restriction/prohibition of manufacturing, processing, distribution, or disposal

Not likely to present an unreasonable risk

- Commercialization can commence after the determination is made
- Section 5(g) – Statement in the FR

Information is insufficient to permit a reasoned evaluation of the risk

- Section 5(e) – Regulation pending more information
- Section 5(e) order
- Testing generally required

Insufficient information to permit a reasoned evaluation **and may present** unreasonable risk

- Section 5(e) – Regulation pending more information
- Section 5(e) order
- Testing generally required

Decision Framework

- "New Chemicals Framework" released for public comment at December 2017 public meeting; describes how EPA is implementing amended TSCA to make decisions on new chemical notices
- Intended conditions of use:
  - The circumstances around manufacture, processing, distribution in commerce, use, or disposal as stated in the submission (original or amended).
  - If conditions of use identified in submissions raise risk concerns, submitters may provide timely written amendments to their submissions addressing those concerns.
  - In general, EPA will consider the amended conditions of use to be the intended conditions of use.

Decision Framework

- Reasonably foreseen conditions of use:
  - Identification of any reasonably foreseen conditions of use will be fact- or knowledge-specific; based on evidence, knowledge, or experience leading EPA to foresee conditions of use different from those described in the submission.
  - If EPA has concerns with intended *and* reasonably foreseen conditions of use, EPA will issue orders followed by significant new use rule (SNURs)
  - If EPA has concerns with reasonably foreseen conditions of use, but *not* with the intended conditions of use, EPA will assess whether those concerns can be addressed through SNURs *without* orders

Decision Framework

Non-order SNUR:

- Considered when EPA has concerns with reasonably foreseen conditions of use, but not with the intended conditions of use as described in a submission (original or amended)
- EPA would make a "not likely to present unreasonable risk" finding for the PMN uses, and use a SNUR to require a Significant New Use Notification (SNUN) for "reasonably foreseen" uses
- EPA would evaluate future SNUNs to determine how best to address risk for those reasonably foreseen uses

Pre-Submission Support

- Two common problems in submissions
  - Information does not allow for refinement of risk assessment
  - Submitter has useful information (e.g., analog data) but it's not provided to EPA
- New *draft* Points to Consider document
  - Issued in November 2017
  - Provides concise guidance to improve PMN submissions – largely based on existing documentation
  - Promotes better submissions, supported by robust pre-submission consultation "program"

Pre-Submission Support

- Pre-consultation meetings
  - Understanding of information useful to EPA's review
  - Helps improve submission quality and program efficiency
- Sustainable Futures Program
  - Provides companies with risk-screening models and training to help develop safer chemicals quickly and cost-effectively.
  - Participating companies become eligible for an expedited EPA pre-manufacture review
  - Contains description of most of the risk assessment process including models and tools
  - Gives insights on what types of engineering processes and releases will be calculated

Pre-Submission Support

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  - Under development
  - Draft outline shared at December 2017 public meeting
  - Will provide submitters with information on how EPA conducts its new chemicals assessments
  - Will help stakeholders determine what forms of regulation and restrictions might be imposed on the manufacture, processing, distribution, use, and/or disposal of a new chemical substance
- Chemical category documents

Next Steps

- Considering public comments from December 2017 public meeting
  - Developing new Questions and Answers for website
- Continuing to implement the Decision Framework
- Utilizing Points to Consider document and encouraging pre-submission consultation
- Improving data systems to enhance ability to track, search and manage new chemical reviews
- Identifying opportunities to streamline processing
- Promoting transparency
- Continuing to improve overall performance

Risk Evaluation
Statutory Requirements

- EPA must establish by rule a process for risk evaluation; signed by Administrator in June 2017
  - Determine if a chemical presents an unreasonable risk of injury to health or the environment under conditions of use
  - Without consideration of cost or other non-risk factors
  - Including unreasonable risk to potentially exposed or susceptible subpopulation(s) determined to be relevant to the evaluation
- This process must be completed within 3 – 3.5 years
- For each risk evaluation completed, EPA must designate a new high-priority chemical
- By December of 2019, EPA must have initiated 20 high-priority chemicals for risk evaluation
  - Additional risk evaluations may come from manufacturer requests

Risk Evaluation
Statutory Requirements

- **First 10** Chemicals – Announced December 19, 2016

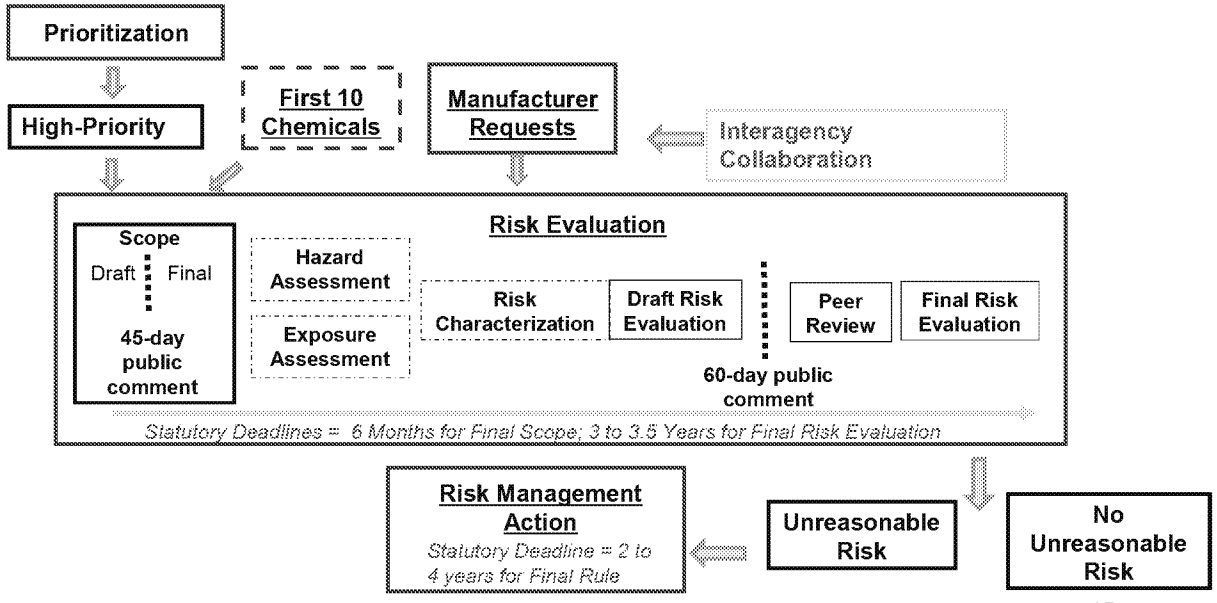
1, 4 Dioxane	Methylene Chloride
1-Bromopropane	N-Methylpyrolidone
Asbestos	Pigment Violet 29
Carbon Tetrachloride	Trichloroethylene
Cyclic Aliphatic Bromide Cluster (HBCD)	Tetrachloroethylene

- **Scope** – Publish within 6 months of initiation; must identify hazards, exposure, conditions of use, potentially exposed or susceptible subpopulation(s) EPA expects to consider
  - Scope documents published June 22, 2017
- **Problem Formulation** documents expected spring 2018

Risk Evaluation
Statutory Requirements

- **Draft Risk Evaluation**
  - Hazard Assessment – identification of types of hazards to human health and/or the environment
  - Exposure Assessment – the duration, intensity, frequency, and number of exposures under the conditions of use
  - Risk Characterization – integration of hazards and exposure into estimates of risk
  - Determination of Unreasonable Risk – does or does not present an unreasonable risk
  - Peer review – all evaluations will be peer reviewed
  - Publication and 30 day public comment period

Risk Evaluation Process and Timeline



Persistent, Bioaccumulative and Toxic Chemicals

- Statute requires a fast-track process for certain PBT chemicals on the TSCA Work Plan, unless a manufacturer requested a risk evaluation by Sep 19, 2016
  - 5 chemicals are getting expedited action
  - Manufacturer requests received for 2 PBT chemicals
- Use and exposure assessment required; no formal risk evaluation
- Rules to reduce exposure, to the extent practicable, must be proposed by June 2019 and finalized 18 months later
- Additional requirements encourage consideration of other PBTs in overall risk evaluation process

For More Information

https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/frank-r-lautenberg-chemical-safety-21st-century-act

Contact EPA at

https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/forms/assessing-and-managing-chemicals-under-tsca

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Message

From: Faeth, Lisa [Faeth.Lisa@epa.gov]
Sent: 2/5/2018 4:40:04 PM
To: Askinazi, Valerie [Askinazi.Valerie@epa.gov]; Barkas, Jessica [barkas.jessica@epa.gov]; Beck, Nancy [Beck.Nancy@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Blair, Susanna [Blair.Susanna@epa.gov]; Blunck, Christopher [Blunck.Chris@epa.gov]; Brown, Sam [Brown.Sam@epa.gov]; Buster, Pamela [Buster.Pamela@epa.gov]; Canavan, Sheila [Canavan.Sheila@epa.gov]; Caraballo, Mario [Caraballo.Mario@epa.gov]; Carroll, Megan [Carroll.Megan@epa.gov]; Cherepy, Andrea [Cherepy.Andrea@epa.gov]; Christian, Myrta [Christian.Myrta@epa.gov]; Corado, Ana [Corado.Ana@epa.gov]; Davies, Clive [Davies.Clive@epa.gov]; DeDora, Caroline [DeDora.Caroline@epa.gov]; Devito, Steve [Devito.Steve@epa.gov]; Dix, David [Dix.David@epa.gov]; Doa, Maria [Doa.Maria@epa.gov]; Drewes, Scott [Drewes.Scott@epa.gov]; Dunton, Cheryl [Dunton.Cheryl@epa.gov]; Ebzery, Joan [Ebzery.Joan@epa.gov]; Edelstein, Rebecca [Edelstein.Rebecca@epa.gov]; Edmonds, Marc [Edmonds.Marc@epa.gov]; Eglsaer, Kristie [Eglsaer.Kristie@epa.gov]; Elwood, Holly [Elwood.Holly@epa.gov]; Farquharson, Chenise [Farquharson.Chenise@epa.gov]; Fehrenbacher, Cathy [Fehrenbacher.Cathy@epa.gov]; Feustel, Ingrid [feustel.ingrid@epa.gov]; Frank, Donald [Frank.Donald@epa.gov]; Gibson, Hugh [Gibson.Hugh@epa.gov]; Gimlin, Peter [Gimlin.Peter@epa.gov]; Gorder, Chris [Gorder.Chris@epa.gov]; Gordon, Brittney [Gordon.Brittney@epa.gov]; Grant, Brian [Grant.Brian@epa.gov]; Gray, Shawna [Gray.Shawna@epa.gov]; Groeneveld, Thomas [Groeneveld.Thomas@epa.gov]; Guthrie, Christina [Guthrie.Christina@epa.gov]; Henry, Tala [Henry.Tala@epa.gov]; Kapust, Edna [Kapust.Edna@epa.gov]; Kemme, Sara [kemme.sara@epa.gov]; Koch, Erin [Koch.Erin@epa.gov]; Krasnic, Toni [krasnic.toni@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Leczynski, Barbara [leczynski.barbara@epa.gov]; Lee, Mari [Lee.Mari@epa.gov]; Leopard, Matthew [Leopard.Matthew@epa.gov]; Liva, Aakruti [Liva.Aakruti@epa.gov]; Lobar, Bryan [Lobar.Bryan@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Menasche, Claudia [Menasche.Claudia@epa.gov]; Moose, Lindsay [Moose.Lindsay@epa.gov]; Morris, Jeff [Morris.Jeff@epa.gov]; Moss, Kenneth [Moss.Kenneth@epa.gov]; Mottley, Tanya [Mottley.Tanya@epa.gov]; Moyer, Adam [moyer.adam@epa.gov]; Myers, Irina [Myers.Irina@epa.gov]; Myrick, Pamela [Myrick.Pamela@epa.gov]; Nazef, Laura [Nazef.Laura@epa.gov]; Ortiz, Julia [Ortiz.Julia@epa.gov]; Owen, Elise [Owen.Elise@epa.gov]; Parsons, Doug [Parsons.Douglas@epa.gov]; Passe, Loraine [Passe.Loraine@epa.gov]; Pierce, Alison [Pierce.Alison@epa.gov]; Pratt, Johnk [Pratt.Johnk@epa.gov]; Price, Michelle [Price.Michelle@epa.gov]; Reese, Recie [Reese.Recie@epa.gov]; Reisman, Larry [Reisman.Larry@epa.gov]; Rice, Cody [Rice.Cody@epa.gov]; Richardson, Vickie [Richardson.Vickie@epa.gov]; Ross, Philip [Ross.Philip@epa.gov]; Sadowsky, Don [Sadowsky.Don@epa.gov]; Santacroce, Jeffrey [Santacroce.Jeffrey@epa.gov]; Saxton, Dion [Saxton.Dion@epa.gov]; Scarano, Louis [Scarano.Louis@epa.gov]; Scheifele, Hans [Scheifele.Hans@epa.gov]; Schmit, Ryan [schmit.ryan@epa.gov]; Schweer, Greg [Schweer.Greg@epa.gov]; Selby-Mohamadu, Yvette [Selby-Mohamadu.Yvette@epa.gov]; Seltzer, Mark [Seltzer.Mark@epa.gov]; Sheehan, Eileen [Sheehan.Eileen@epa.gov]; Sherlock, Scott [Sherlock.Scott@epa.gov]; Simons, Andrew [Simons.Andrew@epa.gov]; Sirmons, Chandler [Sirmons.Chandler@epa.gov]; Slotnick, Sue [Slotnick.Sue@epa.gov]; Smith, David G. [Smith.DavidG@epa.gov]; Stedeford, Todd [Stedeford.Todd@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Symmes, Brian [Symmes.Brian@epa.gov]; Thompson, Tony [Thompson.Tony@epa.gov]; Tierney, Meghan [Tierney.Meghan@epa.gov]; Tillman, Thomas [Tillman.Thomas@epa.gov]; Tomassoni, Guy [Tomassoni.Guy@epa.gov]; Tran, Chi [Tran.Chi@epa.gov]; Vendinello, Lynn [Vendinello.Lynn@epa.gov]; Wallace, Ryan [Wallace.Ryan@epa.gov]; Wheeler, Cindy [Wheeler.Cindy@epa.gov]; Widawsky, David [Widawsky.David@epa.gov]; Williams, Aresia [Williams.Aresia@epa.gov]; Williams, Bridget [Williams.Bridget@epa.gov]; Williamson, Tracy [Williamson.Tracy@epa.gov]; Wills, Jennifer [Wills.Jennifer@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Wolf, Joel [Wolf.Joel@epa.gov]; Wright, Tracy [Wright.Tracy@epa.gov]; Yowell, John [yowell.john@epa.gov]
Subject: News Articles (For EPA Distribution Only)

BNA DAILY ENVIRONMENT REPORT ARTICLES

Access is temporarily unavailable as EPA works through the contract renewal process.

INSIDEEPA.COM ARTICLES

EPA Details Two-Year Plan For 'Lean' Management Opposed By Trump Critics

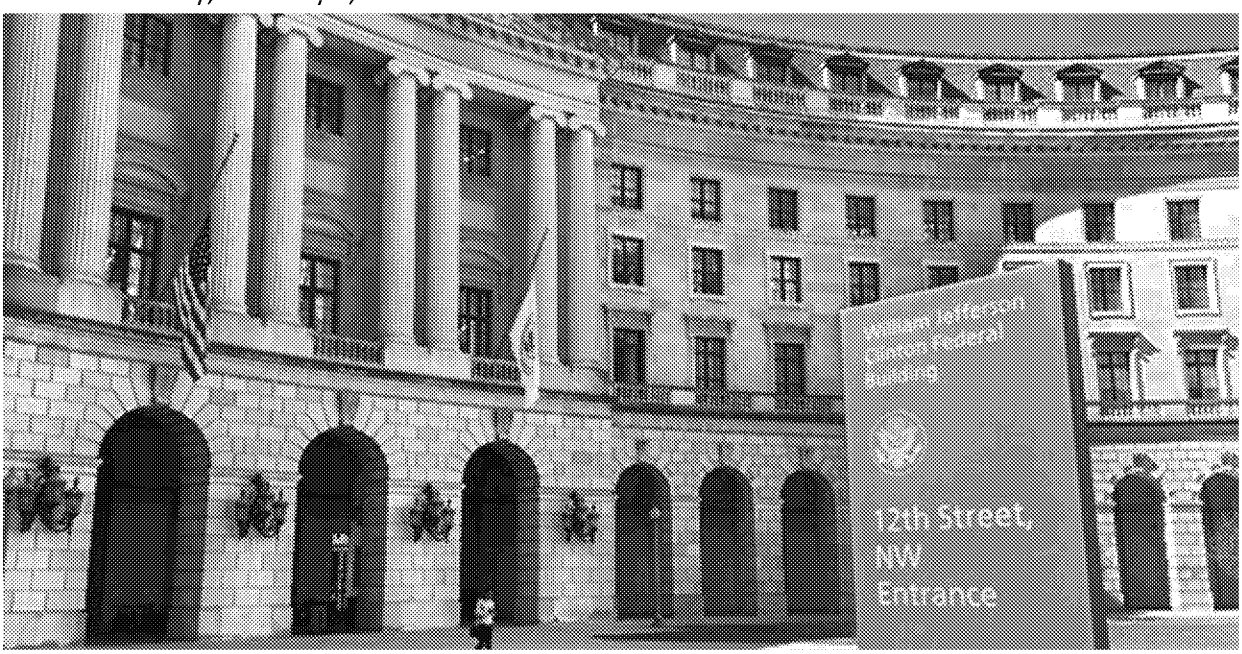
EPA senior officials are detailing a two-year plan for fully implementing a "Lean" management system that they say will overhaul and accelerate agency operations, but some Trump administration critics oppose the approach fearing it will diminish environmental protections and reduce EPA's workforce.

GREENWIRE ARTICLES

Agency posts top leaders' calendars

Kevin Bogardus, E&E News reporter

Published: Friday, February 2, 2018



U.S. EPA is now posting its senior leaders' public calendars online. Robin Bravender/E&E News

U.S. EPA has begun releasing its senior leaders' calendars like it has for Administrator Scott Pruitt.

EPA has posted public calendars on its website for Senate-confirmed officials and regional chiefs.

Like Pruitt's public schedule, the agency will not release top aides' information daily but will instead update it every two weeks, said an EPA official. The official said the documents first went up online this past Friday and will be backdated to Jan. 1.

It is tradition across administrations for EPA to disclose its top officials' public calendars. Former EPA Administrator Gina McCarthy and others on her team released their schedules, typically every morning for that day.

https://www.eenews.net/greenwire/2018/02/02/stories/1060072779

Trump will again try to eliminate CSB — official

Published: Friday, February 2, 2018

President Trump will again seek to zero out the U.S. Chemical Safety Board in his fiscal 2019 budget plan, according to a senior government official familiar with the proposal.

The White House Office of Management and Budget informed the agency in November that the proposal would seek its elimination, the person said.

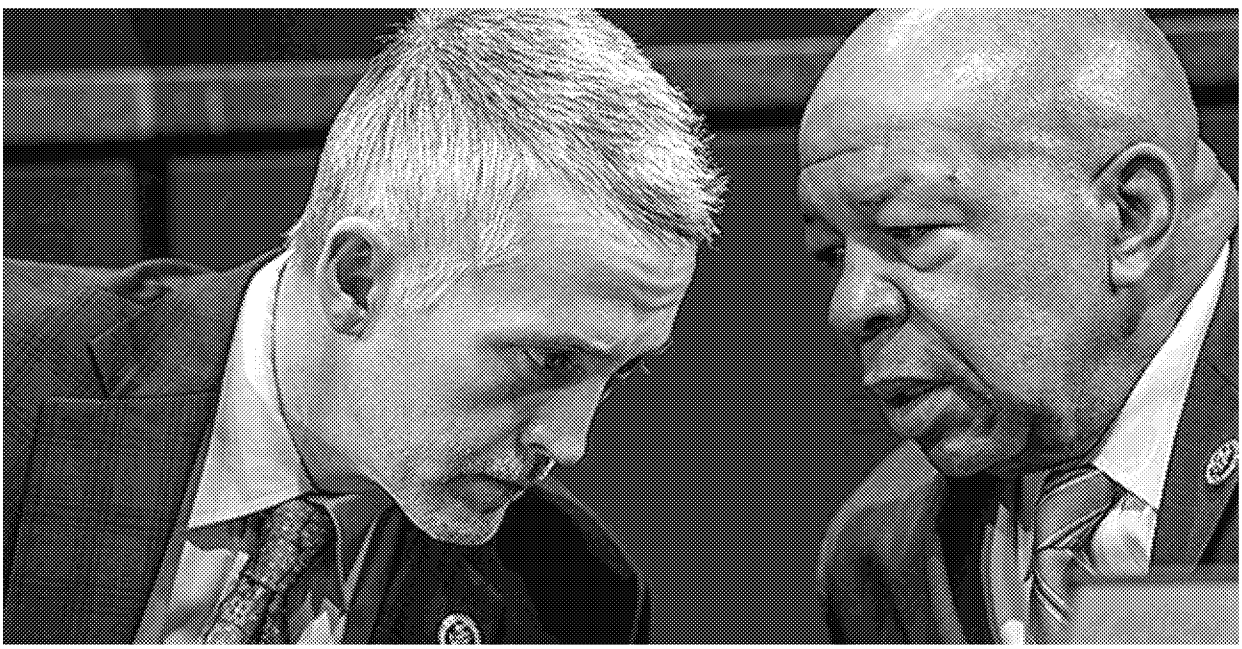
CSB's current budget is $11 million. Trump also sought to cut the independent agency in last year's budget, prompting shock and confusion from board members (*Greenwire*, March 17, 2017).

https://www.eenews.net/greenwire/2018/02/02/stories/1060072767

House watchdogs probe sexual harassment settlements

Kevin Bogardus, E&E News reporter

Published: Friday, February 2, 2018



Reps. Trey Gowdy (R-S.C.) and Elijah Cummings (D-Md.) are investigating how much the federal government has paid to settle sexual harassment cases. J. Scott Applewhite/Associated Press

The House's top watchdogs are asking how much the federal government has paid out to settle employee sexual harassment cases.

In letters sent this week to the departments of Justice and the Treasury, House Oversight and Government Reform Chairman Trey Gowdy (R-S.C.) and ranking member Elijah Cummings (D-Md.) requested information on each payment made from the government's Judgment Fund related to sexual misconduct at federal agencies.

"Every employer should ensure that sexual misconduct, including sexual harassment, sexual assault, and related retaliation, is not tolerated in the workplace and that allegations of sexual misconduct are handled appropriately and timely. The legislative and executive branches of the federal government are no exception," said the lawmakers.

Greens file lawsuit seeking agency FOIA documents

Amanda Reilly, E&E News reporter

Published: Friday, February 2, 2018

Environmental groups have filed a Freedom of Information Act lawsuit over U.S. EPA's delayed responses to FOIA document requests.

Represented by Earthjustice, the Sierra Club alleges that EPA has employed "aggressive" tactics in order to avoid responding to FOIA requests, including through denying requests for fee waivers.

The lawsuit in the U.S. District Court for the Northern District of California seeks records related to any changes in agency FOIA policy under EPA Administrator Scott Pruitt.

"It's time to find out why the public is not getting the information it is supposed to get by law," said Michael Brune, executive director of the Sierra Club, in a statement. "There has never been so much secrecy at the Environmental Protection Agency."

https://www.eenews.net/greenwire/2018/02/02/stories/1060072747

Staffers defend chemical review program under deep scrutiny

Corbin Hiar, E&E News reporter

Published: Friday, February 2, 2018

U.S. EPA's chemical assessment program has powerful critics in Congress, the Trump administration and industry, but that doesn't deter career staffers leading it, they told the National Academies of Sciences, Engineering and Medicine yesterday.

"In Washington, there is a constant cacophony of the beleaguered IRIS program, the dysfunctional IRIS program, all of the things that apparently we can't do well — even though we are the gold standard of risk assessment by all accounts," said EPA staffer Tina Bahadori.

Bahadori has overseen reforms to the Integrated Risk Information System since she took a job as director of EPA's National Center for Environmental Assessment in January 2017.

https://www.eenews.net/greenwire/2018/02/02/stories/1060072761

CHEMICAL WATCH ARTICLES

Risk evaluation, prioritisation addressed in US EPA progress report

2 February 2018 / TSCA, United States

The US EPA has published a mandated progress report on evaluation of existing chemicals under the new TSCA that gives some details on the agency's upcoming timetable.

Published on 31 January, the *2018 Annual Report on Risk Evaluation* notes that the EPA met statutory requirements to issue regulations on risk evaluation and prioritisation of existing chemicals. It also named the first ten chemicals subject to priority assessment and published scoping documents outlining parameters for those evaluations.

Because it had to issue the scoping documents in just six months, the EPA is working on "formulation documents" that will lay out refinements. The new report, the EPA says, "anticipates publishing and taking comments for 45 days on problem formulation documents in early calendar year 2018."

In the final prioritisation rule, the EPA dropped a "pre-prioritisation" process that would have allowed it to identify a pool of potential candidate substances and gather additional data on them before beginning the formal process. Instead, the agency initiated a consultation on how to identify candidates to be designated high and low priority substances that included an 11 December public meeting.

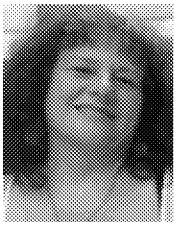
TSCA requires that the prioritisation process takes between nine and 12 months. The progress report says the agency expects to initiate prioritisation for 40 chemicals – at least 20 low priority and 20 high-priority candidates by the end of this calendar year. It also anticipates formally designating those 40 chemicals by 22 December 2019.

This might indicate a change in policy, as a discussion document released ahead of the December meeting said the EPA anticipated naming more than the 20 required "low priority" substances.

Finally, the report says a draft rule on TSCA fees is "undergoing interagency review". This should be published in "early-mid fiscal year 2018". That appears to indicate a target date in February or March. The final rule is expected in "late fiscal year 2018", which ends on 30 September.

The amended law allows the EPA to establish fees to defray 25 percent of the cost of chemical reviews under TSCA.

The draft fee rule will include "estimates of the resources required to undertake risk evaluations", the report says.



Julie A Miller

North American Desk Editor

Related Articles

- NGOs, Democrats decry 'weakened' TSCA framework rules
- EPA names first ten chemicals for new TSCA evaluations

- TSCA: work plan process likely to be basis for chemical prioritisation

Further Information:

- 2018 plan for risk evaluation
- Discussion document

UK law body backs post-Brexit Echa participation

5 February 2018 / REACH, United Kingdom

The UK Environmental Law Association says it would be "highly beneficial" from both "an environmental and a practical perspective" for the UK to retain participation in Echa.

The UKELA is a body of 1,400 environmental law professionals in the UK. Its recent report *Brexit and Environmental Law – the UK and European Cooperation Bodies,* explores the benefits to the country of continued participation in the agency, and the ramifications of no involvement.

It names membership of Echa as a high Brexit priority.

If the UK leaves Echa, it says, the country would need to set up a national agency, agree equivalency rules and mutual recognition and work out procedures to resolve differences.

Continued involvement would help keep the UK aligned with and abreast of constantly evolving EU regulatory development – notably REACH – it says.

Membership would not be possible, it says, without amending underpinning legislation. However, involvement with Echa can be achieved and, alternatively, a cooperation agreement may be possible. In both cases it is unclear to what extent the UK would have to accept the jurisdiction of the European Court of Justice, it says.

In December, Steve Baker, a junior minister in the UK's Department for Exiting the European Union, told MPs that current EU chemicals law, including REACH, will be incorporated into UK law.

A couple of months earlier, a Brexit risk tracker organised by a coalition of environmental NGOs said the UK chemical industry is at a "high level" of risk from the country's departure from the European Union.

Related Articles

- REACH to be converted into UK law, government confirms
- Brexit tracker finds UK chemical industry at 'high risk'

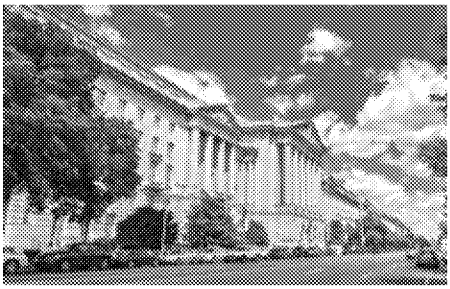
Further Information:

- UKELA report
- Risk tracker

Industry, NGOs clash over US EPA plans for new chemical reviews

Issues include scope of reviews, treatment of additional uses

5 February 2018 / TSCA, United States



Stakeholder comments have hardened the battle lines drawn over the Trump administration's plans for reviewing new chemicals under the revised TSCA.

The public consultation on a proposed review framework document has thrown up several areas of major disagreement between industry and NGOs.

And, to compound the problems facing the EPA, the environmental group the Natural Resources Defense Council (NRDC) has filed a lawsuit against the agency in an effort to block the document's implementation.

The draft framework document was published for comment ahead of a December public meeting on new chemicals policy. It sets out the EPA's intended policy and procedure.

The framework is not a formal regulation, but key issues surrounding it parallel arguments over the EPA's risk evaluation and prioritisation rules, guiding its assessment of existing chemicals under the new TSCA.

The NRDC lawsuit filed on 5 January does not set out legal arguments, but just asks the court to review the new chemical plan. The risk evaluation and prioritisation rules are being challenged in a separate series of lawsuits.

'Conditions of use'

One of the biggest issues in the EPA's plans for both new and existing chemicals is whether the amended law requires the agency to review all potential uses of a chemical, as NGOs argue, or whether it can choose to limit its review to specific uses.

In their written comments, industry organisations argued that the EPA should limit new chemical reviews to the proposed uses set out in the premanufacture notice (PMN) that triggers them.

"The manufacturer of a new chemical should not be held responsible for others' uses or misuses," wrote American Fuel & Petrochemical Manufacturers. "Inclusion of other potential uses requires speculation on the part of the Agency and exceeds the authority granted to EPA."

The EPA's framework calls for addressing "reasonably foreseen" uses, repeating the language in TSCA. At the December meeting, Jeff Morris, director of the agency's Office of Pollution Prevention and Toxics, said the agency will assess "probable" uses of new chemicals.

However, NGOs disagree. "This interpretation has no legal basis," wrote Melanie Benesh, legislative attorney at the Environmental Working Group (EWG). "By definition, the EPA must also include foreseeable uses throughout the entire lifecycle of the chemical from cradle to grave."

Snur-only approach

Also at issue is the EPA's intention to address through significant new use rules (Snurs) situations where a PMN is not problematic but a potential use of the new chemical could raise risk concerns. The agency has most often issued consent orders restricting how the submitter can use a new chemical, followed by a Snur requiring additional review if a different use is proposed.

Industry groups supported the EPA's argument that issuing only Snurs is legal and accomplishes the same goal. But NGOs reiterated their arguments that TSCA requires the agency to issue consent orders, which they believe are more clearly legally binding and give the agency more leverage to regulate additional uses.

And NGOs are also concerned about the implications of issuing "not likely to present an unreasonable risk" findings for new chemicals when there are concerning potential uses not being proposed in the PMN.

Industry groups specifically argued in their comments that the EPA should do that. They say manufacturers should not be held back from bringing a chemical to market based on concerns about potential uses they are not proposing.

The International Fragrance Association North America (Ifrana) even contended that the EPA should not issue Snurs based on potential uses at all. "As a general rule, chemicals subject to Snurs are simply not marketable for nonindustrial uses," Ifrana wrote, due to stigma, record-keeping burdens and knowledge that such chemicals cannot be marketed in Canada.

NGOs say that the EPA should not allow manufacturing of a chemical to start before a Snur is in place preventing more problematic uses.

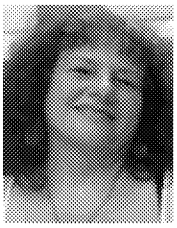
"PMNs, standing alone, are not legally binding on the submitter," the Environmental Defense Fund (EDF) wrote. "Absent a final Snur that is fully in effect, a submitter can at any time engage in conditions of use beyond those identified in the PMN without even notifying EPA."

Deadlines not met

Another issue raised by industry groups is that the EPA has been too conservative in reviewing new chemicals and that the reviews are taking too long.

While the agency is supposed to issue determinations within 90 days, the American Chemistry Council found that for new chemical proposals submitted after the TSCA amendments, it has taken an average of 115 days to issue "not likely to present" findings and an average of 255 days to issue a Snur.

The ACC proposed a series of changes to "streamline" the review process by conducting various required reviews simultaneously and improving communication with submitters.



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North American Desk Editor

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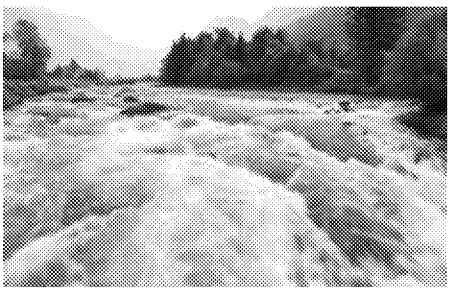
US NGOs urge EPA: ban five PBT substances immediately

Comments argue for an immediate ban on five substances

5 February 2018 / Persistent, bioaccumulative & toxic, TSCA, United States



Environmental groups in the US have vehemently opposed an American Chemistry Council (ACC) suggestion that the EPA should update its criteria for identifying and evaluating "persistent, bioaccumulative and toxic" (PBT) substances before it completes mandated rapid risk management action on five such substances.

In August 2017, the EPA published preliminary information on exposure and use for each of the five PBT chemicals the agency had identified in 2016, and asked for additional data.

In public comments made in response, the groups argue that TSCA's mandate to reduce exposure to these substances "to the extent practicable" requires the EPA to ban their use entirely and take action to reduce exposure to "legacy" uses of the chemicals.

The NGOs also urged the agency to publish regulations requiring disclosure of all uses of the PBT substances rather than relying on the incomplete information currently available and voluntary submissions from industry.

The 2016 TSCA amendments require the EPA to take expedited action on certain PBTs by skipping risk evaluation and proceeding directly to regulation. Proposed risk management rules are due by 22 June 2019.

The agency said in October 2016 it would take action on:

- decaBDE, a flame retardant;
- hexachlorobutadiene (HCBD), used as a solvent and as a hydraulic, heat transfer or transformer fluid;
- pentachlorothiophenol (PCTP), used to make rubber more pliable;

- tris(4-isopropylphenyl) phosphate (IPTPP), used as a flame retardant in consumer products and as a lubricant and hydraulic fluid; and
- 2,4,6-tris(tert-butyl) phenol, an addition in fuels and lubricants.

The ACC argued in its comments that updating the "outdated" PBT criteria from the EPA's workplan, which were used to identify the five priority substances, is consistent with the "scientific requirements" of TSCA and the agency's regulations for implementing it.

But the NGOs said that the criteria are widely accepted and underpin many of the EPA's chemical evaluation activities.

"To now jettison the Congressionally-approved and internationally-accepted Workplan criteria would be not only irresponsible but a reckless reversal of EPA's determination nearly a year ago that the five PBTs" being assessed meet those criteria, wrote Elizabeth Hitchcock, Acting Director of Safer Chemicals Healthy Families (SCHF).

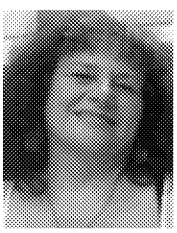
Alaska Community Action on Toxics, the Center for Environmental Health, Earthjustice, the Environmental Health Strategy Center, the Natural Resources Defense Council, and Toxic-Free Future also signed onto those comments.

Robert Stockman, senior attorney at the Environmental Defense Fund (EDF), said the agency should add to the PBT list Pigment Yellow 83, because it meets the law's criteria. He noted that two fragrance chemicals were excluded from rapid action because a manufacturer asked for risk evaluation. There is no evidence that the EPA has begun those evaluations.

Exposure information

In their comments to the August consultation, NGOs argued that the information collected by the EPA thus far underestimates exposure and health risks.

While the EPA document notes that reported US production of decaBDE dropped dramatically between 2012 and 2015, multiple commenters cited studies showing continued presence of the substance in consumer products. For example, under Washington state's disclosure law, the substance was reported 145 times between 2012 and 2017 in children's products.



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- ACC urges EPA to update persistent, bioaccumulative and toxic criteria

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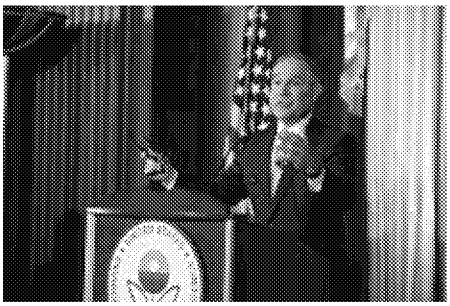
- Comment docket and EPA documentation

Senate committee cross questions EPA Administrator on chemical policy

Scott Pruitt again says agency may reverse policy and consider 'legacy' asbestos uses

5 February 2018 / Priority substances, TSCA, United States



In a Capitol Hill appearance, US EPA Administrator Scott Pruitt appeared to say for a second time that the agency would reverse its policy and consider legacy uses in its review of asbestos.

Mr Pruitt was answering questions at a 30 January hearing convened by the Senate Committee on Environment and Public Works.

The PA Administrator avoided direct answers to questions on how the agency would address chemicals such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), whether it is dragging its feet on priority chemical reviews, and whether it is abandoning proposals to restrict the use of methylene chloride, n-methylpyrrolidone (NMP) and trichloroethylene (TCE).

Senator Jeff Merkley (D-Oregon) expressed concern that the EPA was only focusing on new manufacturing while overlooking "legacy" uses of asbestos.

"I can tell you that the legacy uses you make reference to are very important," said Mr Pruitt, who told another committee in December the issue was under "active consideration".

The framework rules and scoping documents for the first ten substances subject to risk evaluation under TSCA generally exclude "legacy uses" of chemicals from consideration.

Senator Merkley cited a news report that review of the ten priority chemicals was being "slow-walked".

In response, Mr Pruitt said the EPA has adopted TSCA implementation rules as required by the law, and "added resources to address a backlog of chemical reviews". However, those new chemical reviews are unrelated to the review of existing priority chemicals Senator Merkley asked about.

Senator Kirsten Gillibrand (D-New York) asked if a focus on new uses would prevent the EPA from addressing the toxic levels of PFOA and PFOS that have been found in New York and other states.

State policy experts predict that ways of addressing these and related substances will be the biggest emerging chemical regulation issue at state level in 2018. And the FluoroCouncil – a subsidiary of the American Chemistry Council – recently launched a new website seeking to counter the growing controversy.

In December, the EPA announced "a cross-agency effort to address per and polyfluoroalkyl substances (PFASs)," but the plan includes no regulatory action.

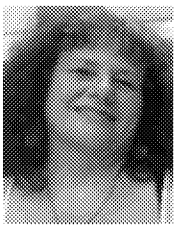
"All the issues we have from PFOA and PFOS are in fact legacy uses and we are going to focus on that," Mr Pruitt told Sen Gillibrand, without further detail.

Senator Tom Carper (D-Delaware) demanded Mr Pruitt commit to finalising within 30 days proposed rules restricting the use of methylene chloride, TCE and NMP.

December updates to the EPA's regulatory agenda moved those rules to the back burner.

"EPA proposed rules banning these chemicals more than a year ago," Senator Carper said. "Recent reports indicate EPA may delay action, which will almost certainly mean more people will get sick and probably some of them will die."

Mr Pruitt said that the chemicals in question are on the priority review list, without addressing the separate proposals for immediate action.



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- US FluoroCouncil website aims to counteract mounting controversy
- US EPA announces 'cross agency' initiative on PFAS
- Restrictions on methylene chloride, NMP, TCE apparently shelved by US EPA

Industry, lawmakers step up Iarc monograph campaign in US

ACC launches coalition in advance of 6 February hearing

5 February 2018 / California Prop 65, Classification, United States

International Agency for Research on Cancer

World Health Organization

As an oversight hearing on the International Agency for Research on Cancer (Iarc) monograph programme prepares to meet, the American Chemistry Council (ACC) has announced it has gathered a coalition of industry and business interests to advocate for "reform."

The meeting on Capitol Hill is scheduled for 6 February.

Iarc's work is controversial because it has regulatory implications in the US. Substances it lists as carcinogens are also listed as such under California's Proposition 65, requiring manufacturers and retailers to warn workers and consumers exposed to them. The ACC also says an Iarc listing affects decisions of retailers.

Campaign

The ACC launched its campaign to alter Iarc's practices more than a year ago. And on 25 January, it announced the Campaign for Accuracy in Public Health Research Coalition. This includes the:

- American Petroleum Institute;
- Chemistry Industry Association of Canada;
- National Association of Manufacturers;
- National Stone, Sand, and Gravel Association;
- Society of Chemical Manufacturers and Affiliates;
- United States Council for International Business; and
- CropLife America.

The coalition aims to address what it says are concerns that have been "raised and reinforced by numerous credible and independent experts about Iarc's efforts to suppress and omit relevant data, as well as the organisation's well-established track-record of manipulating outcomes when it comes to designating key carcinogenic classifications."

The coalition is demanding that Iarc:

- considers actual risk of substances in current use rather than potential hazard;
- fully considers all scientific evidence and give the most weight to those studies that are of the highest quality and greatest relevance to humans;
- establishes "clearly defined, transparent criteria for assessing the quality and reliability of studies";
- increases the transparency of its deliberations and consider stakeholder input;
- discloses all conflicts of interest among the participants and advisors to its working groups; and

- releases monograph findings with supporting documentation rather than releasing short summaries before documentation is made public.

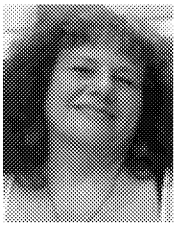
Congressional attacks

Republicans on Capitol Hill have been attacking Iarc's procedures for years. Most recently, three lawmakers threatened to pull US financial support after a testy, and public, exchange of correspondence, and demanded that the agency put forward an official to testify before a hearing in Washington.

The House Science, Space, and Technology Committee has focused specifically on Iarc's 2015 review of glyphosate – the primary ingredient of Monsanto's Roundup herbicide – repeating assertions that have appeared in news media reports alleging irregularities in the controversial decision to classify it as "probably" carcinogenic to humans.

Iarc has apparently not supplied a representative. The witness list for the scheduled hearing includes:

- Anna Lowit, senior science adviser in the US EPA's Office of Pesticide Programs;
- Timothy Pastoor, a toxicologist who became an independent consultant after 17 years at Syngenta Crop Protection;
- Jennifer Sass, senior scientist at the Natural Resources Defense Council; and
- Robert Tarone, (retired) mathematical statistician, US National Cancer Institute and Biostatistics Director, International Epidemiology Institute, who has been critical of Iarc.



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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Comments of Safer Chemicals Healthy Families on Risk Evaluation Scoping Documents for Ten Chemical Substances under the Toxic Substances Control Act

Submitted via Regulations.gov (September 19, 2017)

1,4-Dioxane. Docket ID No.: EPA-HQ-OPPT-2016-0723.

1-Bromopropane. Docket ID No.: EPA-HQ-OPPT-2016-0741.

Asbestos. Docket ID No.: EPA-HQ-OPPT-2016-0736.

Carbon Tetrachloride. Docket ID No.: EPA-HQ-OPPT-2016-0733.

Cyclic Aliphatic Bromide Cluster (Hexabromocyclododecane or HBCD). Docket ID No.: EPA-HQ-OPPT-2016-0735.

Methylene Chloride. Docket ID No.: EPA-HQ-OPPT-2016-0742.

N-Methylpyrrolidone (NMP). Docket ID No.: EPA-HQ-OPPT-2016-0743.

Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f]diisoquinoline-1,3,8,10(2H,9H)-tetrone). Docket ID No.: EPA-HQ-OPPT-2016-0725.

Trichloroethylene (TCE). Docket ID No.: EPA-HQ-OPPT-2016-0737.

Tetrachloroethylene (also known as Perchloroethylene). Docket ID No.: EPA-HQ-OPPT-2016-0732.

INTRODUCTION AND SUMMARY

Safer Chemicals, Health Families (SCHF), Earthjustice, Natural Resources Defense Council (NRDC), Environmental Health Strategy Center, Toxic-Free Future and Asbestos Disease Awareness Organization (ADAO) submit these comments on the scoping documents developed by the Environmental Protection Agency (EPA) on the initial 10 chemicals selected for risk evaluations under the newly enacted Frank R. Lautenberg Chemical Safety for the 21st Century Act (LCSA). These organizations are committed to enhancing the safety of chemicals used in homes, workplaces and products and strongly support effective and health-protective implementation of the LCSA.

Through LCSA, Congress amended the Toxic Substances Control Act (TSCA) to establish a new framework for conducting timely, comprehensive and science-based risk evaluations for chemicals of concern. The law provides that EPA's evaluations must be strictly risk-based and must result in a definitive determination of whether the evaluated substance as a whole presents an unreasonable risk of injury to health and the environment across its life cycle, without regard to cost and other non-risk factors.

Congress wanted EPA to launch the risk evaluation process expeditiously. Accordingly, in section 6(b)(2)(A) of TSCA, it directed EPA to assure that evaluations are initiated within six months of the law's enactment on 10 substances drawn from the 2014 TSCA Workplan list. EPA designated these 10 substances on December 19, 2016,[1] and following a public meeting and comment period, released draft scoping documents on June 22. Soon thereafter, EPA announced that it was developing problem formulation documents on the 10 chemicals and would release them for further comment by the end of the year. It also requested comments on the scoping documents in order to inform its approach to problem formulation.[2]

These comments address general issues common to the 10 chemicals as well as several chemical-specific issues. We are submitting our comments to all ten of the EPA dockets. The comments build on earlier submissions by these groups, including our March 15 comments on the scoping process and our July 24 letter to the Agency providing initial reactions to the 10 scoping documents. We have coordinated with a number of other public health and scientific organizations in developing comments on the scoping documents and generally support their recommendations.

The main messages and key recommendations in our comments are as follows:

- Problem formulation can fill gaps in scoping documents and enhance their depth of analysis but cannot be used to remove uses, exposures and hazards from the risk evaluation scope
- EPA should use problem formulation to provide more detail on the potentially exposed and susceptible subpopulations it will consider and how risks to these subpopulations will be determined
- Problem formulations should also describe EPA's strategies for assessing risks from aggregate and cumulative exposures
- Ongoing use and disposal of chemical products that are no longer being manufactured fall within the TSCA definition of "conditions of use" and must be included in problem formulations and assessed in risk evaluations
- Chemicals with ozone depletion and global warming potential pose environmental and health risks that fall within the scope of TSCA risk evaluations
- EPA risk evaluations should not reassess uses of trichloroethylene (TCE), methylene chloride (MC) and N-Methylpyrrolidone (NMP) that were fully assessed in its proposed section 6(a) rules, although these exposure pathways should be included in its determinations of aggregate exposure to these chemicals
- In the course of TSCA risk evaluations, EPA should not revisit definitive findings in IRIS assessments since these assessments represent the Agency's authoritative, peer reviewed determinations on the health effects of the chemicals they address
- In evaluating workplace risks, EPA should recognize and account for the uneven use and effectiveness of engineering controls, labeling and personal protective equipment in preventing occupational exposure and determine risks to workers in situations where these measures are not in place or ineffective
- EPA should not exclude from the 1,4-dioxane evaluation its production as a byproduct or impurity, which is a significant source of contamination of water sources and cancer risk

[1] 81 Federal Register 91927
[2] 82 Fed. Reg. 31,592 (July 7, 2017).

- In order to apply these general principles and fill other gaps in its scoping documents, these documents must be expanded and strengthened in several specific respects during problem formulation
- EPA should not prejudge the absence of adverse effects for particular end-points at the scoping stage but should defer such conclusions until the systematic review phase of its risk evaluation as the law requires
- Problem formulations should highlight aspects of use and exposure where available information is insufficient and request or require submission of this information by industry and other interested parties
- EPA needs to take stronger steps to limit CBI treatment of critical information during the risk evaluation process so that transparency and public participation in that process are not impaired

I. PROBLEM FORMULATION CAN FILL GAPS IN SCOPING DOCUMENTS AND ENHANCE THEIR DEPTH OF ANALYSIS BUT CANNOT BE USED TO REMOVE USES, EXPOSURES AND HAZARDS FROM THE RISK EVALUATION SCOPE

The 10 chemicals undergoing risk evaluations have widespread and substantial exposure and multiple adverse health effects. Comprehensive and health protective assessments of their safety are essential to safeguard communities and vulnerable populations and to set a precedent for strong and effective implementation of the new law. For this reason, our groups made a significant investment in characterizing the use and exposure profiles of several of the 10 chemicals and provided extensive submissions to the Agency to help inform its scoping documents for these chemicals.

The scoping documents represent a considerable amount of work in a short period of time and provide a helpful starting point for the 10 evaluations. However, the July 7 Federal Register notice announcing the availability of the scoping documents acknowledges that the Agency was unable to process all the information gathered during the scoping process and that the scoping documents were not as "refined or specific" as EPA had hoped. We agree with this assessment and believe that the scoping documents contain serious gaps, lack sufficient information on use and exposure, impose questionable limitations on the risk scenarios to be examined and fail to provide a roadmap to key elements of assessment methodology. These shortcomings reduce the utility of the scoping documents in laying the groundwork for well-informed and rigorous risk evaluations.

Given their limitations, we believe that expanding and strengthening the scoping documents through a problem formulation process is appropriate in this instance. However, neither LCSA nor the recently promulgated risk evaluation process rule refers to or authorizes problem formulation. Because it has no basis in the law, we oppose using problem formulation to narrow the scope of risk evaluations by deleting conditions of use, exposure pathways or health or environmental end-points identified in the June scoping documents. Section 6(b)(4)(D) of amended TSCA provides that, "not later than 6 months after the initiation of a risk evaluation," EPA must "publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use and the potentially exposed or susceptible subpopulations the Administrator expects to consider." EPA met this requirement in its June scoping documents. The law provides no basis for EPA to remove uses, hazards or exposures from a risk

evaluation after its scope has been established in accordance with section 6(b)(4)(D).[3] Since problem formulation is not a recognized step in the risk evaluation process or a substitute for scoping under LCSA, it cannot be used narrow a risk evaluation's scope after-the-fact.

We do support, however, using problem formulation to provide more detail on the conditions of use, potentially exposed and susceptible subpopulations, and exposure pathways that EPA will evaluate as well as further explanation of the methodologies that EPA will use in its analysis of these and other risk assessment elements. This will help better structure the risk evaluations, assure that all relevant information is considered, and characterize more fully the conditions of use to be evaluated – without narrowing the risk evaluation scope.

II. EPA SHOULD USE PROBLEM FORMULATION TO PROVIDE MORE DETAIL ON THE POTENTIALLY EXPOSED AND SUSCEPTIBLE SUBPOPULATIONS IT WILL CONSIDER AND HOW RISKS TO THESE SUBPOPULATIONS WILL BE DETERMINED

One area that would benefit from greater elaboration during problem formulation is the identification of potentially exposed or susceptible subpopulations that require consideration in risk evaluations under TSCA section 6(b)(4)(F). The scoping documents provide nearly identical general "boilerplate" descriptions of such subpopulations. Further particulars on the size, geographic location, demographic characteristics and exposure profile of each subpopulation EPA has identified would provide helpful assurance that the risks to that subpopulation will be characterized with the rigor that TSCA requires.

It is also critical for EPA to spell out the methodology it intends to use to determine the nature and magnitude of the risks that chemicals pose to each subpopulation. Such subpopulations are often comprised of low income and/or people of color and exposed to a disproportionate share of pollution, environmental hazards, and social and economic stressors. Multiple exposures to chemical and non-chemical stressors collectively increase the risk of harm, combined with synergistic effects with other health stressors such as limited access to quality health care.[4,5] EPA's risk evaluations need to fully account for these factors and its problem formulations should explain how it intends to do so.

In regard to greater susceptibility, the following are well-known factors that increase biologic sensitivity or reduce resilience to exposures,[6,7] and should be considered consistently for all 10 chemicals to identify susceptible subpopulations:

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[3] EPA's final risk evaluation rule, in contrast to its proposal, would permit the Agency to select which conditions of use to include in risk evaluation scopes as opposed to including all such uses. 82 Fed. Reg. 33,726 (July 20, 2017). Our groups argued in their comments on the proposal that the law required the Agency to address all conditions of use in its risk evaluations, as was recognized in the Agency's original proposal. Along with several other groups, we are challenging EPA's contrary interpretation in its petition for judicial review of the risk evaluation rule. Regardless of the outcome of this challenge, we believe that EPA has no basis to narrow the risk evaluation to exclude conditions of use once they have been included in its scope.

[4] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff. 2011;30(5):879–87.

[5] Vesterinen HM, Morello-Frosch R, Sen S, Zeise L, Woodruff TJ. Cumulative effects of prenatal-exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the human and animal evidence. Meliker J, editor. PLoS One. 2017 Jul 12;12(7):e0176331.

[6] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff. 2011;30(5):879–87.

Intrinsic/ endogenous factors

- Genetic polymorphisms/ genetics/ genetic makeup
- Health status/ nutritional status/ disease status/ pre-existing conditions
- Prenatal life stage
- Age

Extrinsic factors

- Multiple exposures/ co-exposures
- Race/ ethnicity
- Socioeconomic status (SES)

For example, the prenatal life stage is the most sensitive to developmental and reproductive toxicants, and women of childbearing age should be considered as a susceptible subpopulation for any chemical with such hazards. However, women of reproductive age are not identified as a potential susceptible subpopulation in the scoping documents for pigment violet 29, TCE, NMP, PERC, or HBCD, even though EPA will consider reproductive and developmental toxicity hazards for these chemicals. This omission should be corrected during problem formulation.

III. PROBLEM FORMULATION MUST DESCRIBE EPA'S STRATEGIES FOR ASSESSING RISKS FROM AGGREGATE AND CUMULATIVE EXPOSURES

Problem formulation should also address more fully how EPA intends to address the risks resulting from cumulative and aggregate exposures to each of the 10 chemicals. The scoping documents provide minimal discussion of this essential aspect of risk evaluation design.

Section 6(b)(4)(F)(ii) requires risk evaluations to describe whether aggregate or sentinel exposures to a chemical were considered and the basis for that consideration. To properly apply either or both of these approaches in a risk evaluation, EPA must determine in advance what methodology it will employ and then incorporate it in the risk evaluation design in sufficient detail to describe the key data sources it will use to assess exposure and how they will be used. The scoping documents fail to do this. EPA should remedy this gap in problem formulation.

We believe aggregate exposure assessment will be required for all of the 10 chemicals.[8] The focus of the new law is on determining risk based on all relevant pathways and sources of exposure for the general population and vulnerable subpopulations throughout a chemical's life cycle. Thus, under section 6(b)(4)(F)(i), EPA must "integrate and assess available information on hazards and exposures for *the conditions of use* of the chemical substance" and, under section 6(b)(4)(F)(iv), must "take into account, where relevant, the likely duration, intensity, frequency and number of exposures under *the conditions of use* of the chemical substance." This emphasis on integrating risk and exposure factors across a chemical's conditions of use necessarily requires the Agency to identify all sources of exposure that may affect the general population or specific subpopulations and to determine the overall levels, frequency

[7] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009.

[8] When analyzing aggregate exposures, "sentinel exposure" may be considered simultaneously, where appropriate. However, these are not mutually exclusive and EPA should not incorporate sentinel to the exclusion of aggregate.

and duration of exposures by each population or subpopulation resulting from this combination of pathways.[9]

EPA has applied the tools of "aggregate exposure assessment" successfully in several programs. For example, the 1996 Food Quality Protection Act (FQPA) directs EPA to examine aggregate exposures when issuing or renewing tolerances for pesticides in food and EPA has longstanding guidance for doing aggregate risk and exposure assessments to meet this requirement.[10]

During problem formulation, EPA should develop a roadmap for each of the 10 chemicals showing what steps it is taking to gather the necessary information for aggregate exposure assessment and how it will calculate or estimate the combined exposures resulting from multiple pathways or uses for the general population and potentially exposed or susceptible subpopulations.

Problem formulations should also address whether and how EPA will use "cumulative risk" methodologies for the first 10 risk evaluations. This, too, is an area that EPA has addressed in several guidance documents.[11] The Agency defines "cumulative risk" as "the combined risks from aggregate exposures (i.e., multiple route exposures) to multiple agents or stressors" and has explained that:

> "In cumulative risk assessments that examine risks posed by multiple chemicals, exposure assessments evaluate a population's chemical exposures through multiple routes of exposure over time. Such assessments may encompass multiple exposure timeframes in which the timing and intensity of exposures to different chemicals are examined relative to each other. It is also important to determine whether the exposures to multiple chemicals can lead to toxicokinetic interactions or toxicodynamic interactions. In addition to providing information about multiple chemical exposures in the general population, these exposure assessments identify potentially susceptible or vulnerable subpopulations in the study area and potentially unique pathways of exposure in those subpopulations."[12]

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[9] Exposures from TSCA-exempt uses such as personal care products or biocides should also be included in scoping documents and risk evaluations because of the need to account for their contribution to aggregate risk, even though regulatory authority over these products is not available under TSCA but derives from other laws administered by EPA or agencies such as FDA. This is now standard practice in implementing the Food Quality Protection Act (FQPA). The scoping documents contain limited and incomplete information on exposures to the listed chemicals from non-TSCA uses.

[10] https://www.epa.gov/sites/production/files/2015-07/documents/aggregate.pdf

[11] E.g., *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity.* U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC. (2002) Available at http://www.epa.gov/oppfead1/trac/science/cumulative_guidance.pdf; *Framework for Cumulative Risk Assessment,* U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/600/P-02/001F (2004). Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944.

[12] EPA National Center for Environmental Assessment, *Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document,* at xxviii (August 2007).

The importance of examining risks posed by multiple chemicals with overlapping pathways of exposure and common adverse health effects was also underscored by the National Academy of Sciences (NAS) in its Phthalates and Cumulative Risk report.[13]

We recommend that, in its problem formulations, EPA should commit to perform cumulative risk assessments whenever a population or subpopulation exposed to the subject chemical is also exposed to other chemicals that have similar health effects. In this situation, total risk to the relevant population or subpopulation will be a function not just of exposure to the subject chemical in isolation but of combined exposure to that chemical and other chemicals which have additive or synergistic health effects.

A compelling case for examining cumulative risks will exist where EPA is in parallel conducting risk evaluations on multiple chemicals within a class that have similar chemical structures, conditions of use and adverse health effects. An example of such a grouping is the four solvents (TCE, PERC, MC and NMP) among the initial 10 chemicals: not only is it likely that workers and consumers are exposed to all or some of these solvents simultaneously but their common hazards (i.e. neurotoxicity, reproductive toxicity) are likely to magnify the risks of such concurrent exposures. The problem formulations for these four chemicals should recognize the need to examine the cumulative risks they present and describe how EPA will evaluate cumulative risk scenarios.

IV. ONGOING USE AND DISPOSAL OF CHEMICAL PRODUCTS THAT ARE NO LONGER BEING MANUFACTURED FALL WITHIN THE TSCA DEFINITION OF "CONDITIONS OF USE" AND MUST BE ASSESSED IN RISK EVALUATIONS

Several of the 10 chemicals – asbestos, perchloroethylene (PERC), TCE, MC, carbon tetrachloride (CTC) and hexabromocyclododecane (HBCD) – contribute to ongoing exposure and risk as a result of historical manufacturing and processing activities that have been discontinued. In many cases, the current and foreseeable risks associated with these activities are significant. Nonetheless, the scoping documents provide limited information about these risk and exposure scenarios and take the position that they are outside the scope of risk evaluations except possibly as a source of information about aggregate exposure. Each scoping document contains this statement:

> "EPA interprets the mandates under section 6(a)-(b) to conduct risk evaluations and any corresponding risk management to focus on uses for which manufacture, processing, or distribution in commerce is intended, known to be occurring, or reasonably foreseen (i.e., is prospective or on-going), rather than reaching back to evaluate the risks associated with legacy uses, associated disposal, and legacy disposal, and interprets the definition of "conditions of use" in that context. For instance, the conditions of use for purposes of section 6 might reasonably include the use of a chemical substance in insulation where the manufacture, processing or distribution in commerce for that use is prospective or on-going, but would not include the use of the chemical substance in previously installed insulation, if the manufacture, processing or distribution for that use is not prospective or on-going. In other words, EPA interprets the risk evaluation process of section 6 to focus on the continuing flow of chemical

[13] National Research Council. Committee on the Health Risks of Phthalates, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies. 2008. Phthalates and cumulative risk assessment: the task ahead. Washington, D.C.: National Academies Press.

substances from manufacture, processing and distribution in commerce into the use and disposal stages of their lifecycle. That said, in a particular risk evaluation, EPA may consider background exposures from legacy use, associated disposal, and legacy disposal as part of an assessment of aggregate exposure or as a tool to evaluate the risk of exposures resulting from non-legacy uses."[14]

We believe that EPA is incorrectly interpreting the provisions of LCSA. The definition of "conditions of use" in section 3(4) covers the "circumstances . . . under which a chemical substance is . . . known or reasonably foreseen to be . . . used or disposed of." Where a chemical is performing an ongoing *in situ* function as a result of previous manufacturing and processing activity, that function comprises a current "use" of the chemical that is "known" to be occurring.

For example, although asbestos may no longer be sold as insulation, the asbestos insulation installed in millions of US buildings continues to perform insulating functions and thus is a current ongoing "use" of asbestos. Installed asbestos-containing building materials (ACBMs) represent one of the largest sources of asbestos accessible to the general public in the US, and the largest asbestos-exposed population consists of people who occupy buildings and homes with ACBMs. Maintenance and construction activities involving ACBMs are also frequent and widespread and account for the largest present-day increase in mesothelioma illness and death in the US.[15]

Similarly, the Healthy Building Network estimates there are 66-132 million pounds (30,000-60,000 metric tons) of HBCD in insulation in existing buildings.[16] These ongoing insulation uses are and will continue to be critical sources of ongoing exposures. HBCD is also present in cars and furniture as a flame retardant and its use in these long-lived consumer articles will contribute to ongoing exposures for years to come.[17]

Equally important, the disposal of building materials or consumer products containing asbestos or HBCD is an ongoing occurrence as buildings are torn down or remodeled and cars and furniture are replaced. Thus, the resulting releases into the environment and communities comprise a "circumstance . . . under which [these chemicals] are . . . known or reasonably foreseen to be . . . disposed of." As "conditions of use" within the TSCA definition, these activities and the risks they present are likewise required to be addressed in risk evaluations under section 6(b). For both chemicals, the immediate and long-term exposures associated with disposal of *in situ* building materials and products are likely to be widespread and significant well into the future.

To exclude from risk evaluations ongoing and future exposures from *in situ* uses of discontinued products would create a sizable gap in the life-cycle assessments of risk that Congress directed EPA to conduct under the new law. This would deprive the public, scientists and regulators of a comprehensive

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[14] EPA, *Scope of the Risk Evaluation for Asbestos*, June 2017, at 8.

[15] US CDC study, "Malignant Mesothelioma Mortality – United States 1999 to 2005."

[16] Safer Chemicals, Healthy Families et al. Comments to the U.S. Environmental Protection Agency (EPA) on the Scope of its Risk Evaluation for the TSCA Work Plan Chemicals: CYCLIC ALIPHATIC BROMIDE CLUSTER or HEXABROMOCYCLODODECANE (HBCD). March 15, 2017. https://healthybuilding.net/uploads/files/saferchemicals-hbcd.pdf

[17] For chemicals like TCE and PERC, the uses that contributed to widespread contamination of groundwater and drinking water may in fact be uses for which these chemicals are still being sold, requiring EPA to include them in its risk evaluations even under its narrow interpretation of the law.

picture of one of the largest sources of continuing and future risk. One consequence would be that EPA would lack the scientific basis to ban resumption of the sale and distribution of discontinued products containing asbestos, HBCD and similar chemicals despite the unreasonable risks that they present. In addition, decision-makers would be unable to reduce ongoing exposures and impose safeguards against unsafe disposal because they would lack a meaningful risk evaluation to inform these actions. Just as TSCA provides authority to evaluate the risks associated with ongoing exposures from discontinued activities, so it gives EPA the authority under section 6(a) to reduce these risks, yet the Agency would be stymied by the absence of a risk evaluation that provides a basis for such regulation.[18]

In short, EPA must characterize and assess ongoing exposures from the use and disposal of discontinued products and determine the risks they present as part of its risk evaluations on the initial 10 chemicals. The scoping documents provide virtually no discussion of these sources of exposure to the 10 chemicals. Nothing in the law allows EPA to exclude these risks from its evaluations. EPA must correct this omission during problem formulation.

V. OZONE DEPLETION AND GLOBAL WARMING POTENTIAL POSE ENVIRONMENTAL AND HEALTH RISKS THAT FALL WITHIN THE SCOPE OF TSCA RISK EVALUATIONS

In earlier submissions, SCHF and its members highlighted data showing the high ozone depleting potential of MC, CTC and 1-Bromopropane (1-BP).[19] The scoping documents do not address these properties of the three chemicals. Nor do they examine the global warming potential (GWP) of any of the 10 chemicals. These omissions conflict with the express purpose of risk evaluations under section 6(b)(4)(A): to "determine whether a chemical substance presents an unreasonable risk of injury to health *or the environment"* (emphasis added). They also fail to meet the Agency's obligation under section 6(b)(4)(F)(i) to "integrate and assess information . . . that is relevant to specific risks of injury to health *or the environment"* (emphasis added). Ozone depletion and global warming potential clearly pose risks to the environment and they are also recognized risk factors for human health.[20,21] Nothing in the law allows EPA to exclude these risks from its evaluations.

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[18] For some chemicals like lead and asbestos, other laws administered by EPA address handling and disposal of *in situ* materials. The Agency may be able to refer the findings of its risk evaluations to the programs implementing these laws under TSCA section 9(b) in lieu of further regulation under section 6. However, there are no existing laws that address ongoing exposure from use and disposal of discontinued products containing HBCD, perfluorinated chemicals and other substances and therefore the availability of the protections afforded under section 6 of TSCA may be critical to addressing their risks.

[19] See Comments of Safer Chemicals Healthy Families on Risk Evaluation Scoping Documents for Ten Chemical Substances under the Toxic Substances Control Act, March 15, 2017.

[20] The human health risks of ozone depletion are well recognized by the Agency and documented, at least in part, on EPA's webpage, "Health and Environmental Effects of Ozone Layer Depletion:" "Ozone layer depletion increases the amount of UVB that reaches the Earth's surface. Laboratory and epidemiological studies demonstrate that UVB causes non-melanoma skin cancer and plays a major role in malignant melanoma development. In addition, UVB has been linked to the development of cataracts, a clouding of the eye's lens." https://www.epa.gov/ozone-layer-protection/health-and-environmental-effects-ozone-layer-depletion (Accessed 9-18-17)

[21] The human health risks of global warming were well recognized and documented, at least in part, by the agency prior to the arrival of Administrator Pruitt, as outlined in the legacy pages at: https://19january2017snapshot.epa.gov/climate-impacts/climate-impacts-human-health_.html While that page is being updated, "...to reflect EPA's priorities under the leadership of President Trump and Administrator Pruitt," the Agency still notes, "Climate change is having direct and indirect impacts on the health of people. More extreme

The EPA Office of Air and Radiation (OAR) has considerable expertise in both ozone depletion and global warming and has assessed some (but not all) of the 10 chemicals from the perspective of these concerns. OAR can help OCSPP draw on this prior work for its TSCA risk evaluations and perform new assessments for those chemicals whose ozone depletion and global warming impacts have not previously been examined. By addressing these impacts in TSCA risk evaluations, EPA will fulfill the law's goal of providing a comprehensive picture of environmental and health risks across the chemical's life cycle. In particular cases, it may also highlight contributors to ozone depletion and global warming that have been overlooked and may warrant restriction. Whether these impacts can be adequately addressed under the Clean Air Act (CAA) or under TSCA need not be determined in the risk evaluation itself and can be deferred to the later evaluation of risk management options under section 6(a).

VI. EPA RISK EVALUATIONS SHOULD NOT REASSESS USES OF TCE, MC AND NMP THAT WERE FULLY ASSESSED IN ITS PROPOSED SECTION 6(a) RULES

EPA has proposed to ban certain uses of TCE, MC and NMP under section 6(a) of amended TSCA.[22] As the basis for these proposed rules, EPA conducted comprehensive exposure and risk assessments on the targeted uses of the three chemicals. These assessments were subject to public comment and peer review both during their development and again as part of the rulemaking process.

In its scoping documents for the three chemicals, EPA indicates that it intends to rely on the completed assessments and will not "reassess" the targeted uses.[23] We strongly agree with this approach. It would be counterproductive for the Agency reopen these assessments for yet another round of public input and to redo the extensive analysis they contain simply so industry commenters can have another bite at the apple on findings they dislike. Moreover, we believe that the next step in the rulemakings is for EPA to issue final rules as quickly as possible. These rules, once issued, should close the book on the targeted uses and enable EPA to focus its risk evaluations on uses that have not yet been assessed. In its more comprehensive risk evaluations, however, EPA should incorporate its earlier assessments so that the exposures they describe can be accounted for in determining aggregate exposure to the three chemicals.

VII. EPA SHOULD NOT REVISIT DEFINITIVE FINDINGS IN IRIS ASSESSMENTS, WHICH REPRESENT THE AGENCY'S AUTHORITATIVE PEER-REVIEWED DETERMINATIONS OF THE HEALTH EFFECTS OF CHEMICALS

Five of the 10 chemicals – TCE, MC, CTC, PERC and 1,4-dioxane – have been assessed under the EPA Integrated Risk Information System (IRIS). The IRIS process is the Agency's authoritative mechanism for reviewing available studies, characterizing the health effects of chemicals and identifying concentrations below which these chemicals are not likely to cause adverse effects. IRIS assessments typically reflect

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weather events, heat waves, spread of infectious diseases and detrimental impacts on air and water quality are having impacts on our health." https://www.epa.gov/climate-research/human-health-and-climate-change-research (accessed 9-18-17).

[22] Trichloroethylene (TCE); Regulation of Use in Vapor Degreasing under TSCA Section 6(a), 82 Fed. Reg. 7432 (Jan. 19, 2017); Trichloroethylene; Regulation of Certain Uses under TSCA § 6(a), 81 Fed. Reg. 91592 (Dec. 16, 2016) and Methylene Chloride and N-Methylpyrrolidone; Regulation of Certain Uses under TSCA Section 6(a), 82 Fed. Reg. 7464 (Jan. 19, 2017).

[23] See, e.g., EPA. *Scope of the Risk Evaluation for Trichloroethylene,* June 2017, at 33.

years of work by EPA scientists, multiple rounds of public comment, inter and intra-agency consultation, and extensive peer review, often by the Agency's independent Science Advisory Board (SAB) or the National Academy of Sciences (NAS).

Where EPA is conducting a TSCA risk evaluation of a chemical that has already been assessed under IRIS, the conclusions of the IRIS assessment should be presumed to be applicable to the TSCA evaluation as a definitive statement by the Agency of the best available science. To revisit IRIS findings would be inefficient and resource-intensive at a time when the Agency is struggling with workforce and budget reductions. It would also make the three-year statutory deadline for completing risk evaluations even more challenging by greatly expanding the scope of EPA's work effort. Most significantly, reopening IRIS findings would prolong scientific uncertainty on issues that have been addressed and resolved through an authoritative, transparent and inclusive EPA process. Like other Agency actions, IRIS assessments often give rise to differences of opinion and some stakeholders may be disappointed by the outcome. But this does not mean that EPA should reinvent the wheel and provide another bite at the apple on scientific determinations that have been made after thorough deliberation and a robust process.

In sum, the problem formulation documents on the 10 chemicals should make clear that EPA's risk evaluations will rely on previous IRIS assessments in determining health effects that those assessments address.

VIII. IN EVALUATING WORKPLACE RISKS, EPA SHOULD RECOGNIZE THE UNEVEN USE AND EFFECTIVENESS OF ENGINEERING CONTROLS, LABELING AND PERSONAL PROTECTIVE EQUIPMENT IN PREVENTING OCCUPATIONAL EXPOSURE

Several scoping documents indicate that, in its approach to occupational exposure analysis, EPA will "[c]onsider and incorporate applicable engineering controls and/or personal protective equipment into exposure scenarios."[24] These measures are certainly relevant factors in analyzing occupational exposures. However, it is essential that EPA not presume that they will be effective in preventing exposure in all workplaces and for all employees. In many cases, they may in fact provide limited protection, particularly for short-term poorly trained workers in small shops and workers whose English language skills are challenged.

In its proposed section 6(a) rules for TCE, MC and NMP, EPA explained at some length why label warnings and instructions are not uniformly read, comprehended or followed and thus provide limited protection. This was not a mere opinion on EPA's part but the result of an examination of nearly fifty studies.[25] Based on this review, EPA's conclusions as described in its initial TCE rulemaking were as follows:

> "The Agency determined that warning labels and instructions alone could not mitigate the risks to the extent necessary so that TCE no longer presents the identified unreasonable risks to users. The Agency based this determination on an analysis of 48 relevant studies or meta-analyses, which found that consumers and professionals do not consistently pay attention to

[24] See, for example, US EPA (2017). Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster. Pg. 45

[25] OPPT summarized these studies in a paper entitled *The Effectiveness of Labeling on Hazardous Chemicals and Other Products* (March 2016)(Ref. 33 in rulemaking docket).

labels; consumers and professional users often do not understand label information; consumers and professional users often base a decision to follow label information on previous experience and perceptions of risk; even if consumers and professional users have noticed, read, understood, and believed the information on a hazardous chemical product label, they may not be motivated to follow the label information, instructions, or warnings; and consumers and professional users have varying behavioral responses to warning labels, as shown by mixed results in studies."[26]

In the TCE vapor degreasing proposal, EPA further concluded that comprehension of warnings would be unusually challenging because of the complexity of the information conveyed:

> "EPA found that presenting information about TCE on a label would not adequately address the identified unreasonable risks because the nature of the information the user would need to read, understand, and act upon is extremely complex. It would be challenging to most users to follow or convey the complex product label instructions required to explain how to reduce exposures to the extremely low levels needed to minimize the risk from TCE. Rather than a simple message, the label would need to explain a variety of inter-related factors, including but not limited to the use of local exhaust ventilation, respirators and assigned protection factor for the user and bystanders, and time periods during pregnancy with susceptibility of the developing fetus to acute developmental effects, as well as effects to bystanders. *It is unlikely that label language changes for this use will result in widespread, consistent, and successful adoption of risk reduction measures by users and owners.*[27]

Similarly, EPA cautioned that "there are many documented limitations to successful implementation of respirators", including these well-known problems: [28]

> "Not all workers can wear respirators. Individuals with impaired lung function, due to asthma, emphysema, or chronic obstructive pulmonary disease for example, may be physically unable to wear a respirator. Determination of adequate fit and annual fit testing is required for a tight fitting full-face piece respirator to provide the required protection. Also, difficulties associated with selection, fit, and use often render them ineffective in actual application, preventing the assurance of consistent and reliable protection, regardless of the assigned capabilities of the respirator. Individuals who cannot get a good face piece fit, including those individuals whose beards or sideburns interfere with the face piece seal, would be unable to wear tight fitting respirators. In addition, respirators may also present communication problems, vision problems, worker fatigue and reduced work efficiency (63 FR 1156, January 8, 1998). According to OSHA, 'improperly selected respirators may afford no protection at all (for example, use of a dust mask against airborne vapors), may be so uncomfortable as to be intolerable to the wearer, or may hinder vision, communication, hearing, or movement and thus pose a risk to the wearer's safety or health. (63 FR 1189-1190).'"

EPA based these conclusions on expert analyses by OSHA, which has extensive experience with respirators under its workplace standards.

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[26] 81 FR at 91601.
[27] 82 FR 7441 (emphasis added)
[28] 82 FR 7445

The problem formulation documents should explicitly recognize that industrial hygiene controls do not necessarily provide reliable and effective protection from exposure and that the adequacy of these controls needs to be examined on a case-by-case basis in the context of the specific establishments where the chemical is used, the makeup of the worker population in these establishments and the diligence of employers in implementing workplace controls. During problem formulation, EPA should elaborate on how these considerations will be applied for the 10 chemicals.

More generally, when considering occupational exposures, EPA needs to recognize and account for differences in levels of exposure, workplace practices and susceptibility that result in significant gradations in risk, even within a single workplace. In workplaces where chemicals and chemical products are used, exposures typically occur most intensely among a highly exposed subgroup, rather than uniformly across the population of workers. In a vehicle repair shop, for example, chemical-intensive tasks on brakes, engines, and drive-train components are performed by a subset of workers who experience high levels of exposure to aerosolized degreasing solvents, whereas other workers in the same shop who perform diagnostic or electrical work, for example, experience little or no exposure to these solvents. To effectively characterize the "conditions of use" among workers, EPA must account for the levels and duration of exposure—and therefore risk—that occurs within highly exposed subgroups as a consequence of actual workplace conditions, rather than relying on an "average" estimated exposure across a population of workers, based on an assumption of "intended" use.

IX. EPA SHOULD NOT EXCLUDE FROM THE 1,4-DIOXANE EVALUATION ITS PRODUCTION AS A BYPRODUCT OR IMPURITY, WHICH IS A SIGNIFICANT SOURCE OF CONTAMINATION OF WATER SOURCES

The scoping document for 1,4-dioxane takes the unusual approach of precluding any consideration of this substance's manufacture as a byproduct or impurity in EPA's risk evaluation:

> "In the case of 1,4-dioxane, EPA anticipates that production of 1,4-dioxane as a by-product from ethoxylation of other chemicals and presence as a contaminant in industrial, commercial and consumer products will be excluded from the scope of the risk evaluation. These 1,4-dioxane activities will be considered in the scope of the risk evaluation for ethoxylated chemicals. EPA believes its regulatory tools under TSCA section 6(a) are better suited to addressing any unreasonable risks that might arise from these activities through regulation of the activities that generate 1,4-dioxane as an impurity or cause it to be present as a contaminant than they are to addressing them through direct regulation of 1,4-dioxane"[29]

This is a deeply flawed approach that will weaken the 1,4-dioxane risk evaluation and result in inadequate risk reduction during any subsequent rulemaking under section 6(a).

1,4-dioxane is a probable carcinogen that has contaminated drinking water and groundwater in multiple parts of the country, eliciting expressions of concern from many public officials and communities. A recent analysis of data from EPA-mandated monitoring indicates that water supplies for more than 7

[29] Scope of the Risk Evaluation for 1,4-Dioxane, at 8 (June 2017)

million Americans in 27 states contain 1,4-dioxane at levels above those that EPA and other agencies believe present an acceptable cancer risk.[30]

1,4-dioxane's presence in drinking water and groundwater is linked to several pathways of release into the environment. In addition to its manufacture as a chemical product, 1,4-dioxane is a byproduct of plastic production and other chemical manufacturing processes utilizing ethoxylation. Due to its production as a byproduct, it is present as an impurity in several industrial, commercial and consumer products. 1,4-dioxane often is found in the wastewater discharged by industrial facilities and POTWs. Its presence in wastewater is likely attributable not only to intentional production and use activities but to the use and disposal of products in which it is present as an impurity.

If 1,4-dioxane's manufacture as a byproduct and presence in products and waste streams as an impurity are excluded from EPA's risk evaluation, it will have no basis for accounting for these sources of environmental release and will be unable to characterize their contribution to levels of the chemical found in drinking water, surface water and ground water. This will make its assessment of the extent and causes of water contamination incomplete and undermine its ability to conduct an informed evaluation of the options for reducing contamination and risk. Any action it later decides to take under section 6 will thus be based on inadequate information and analysis and, as a result, may be ineffective and under-protective.

Manufacture as a byproduct is plainly within the definition of "conditions of use" in section 3(4) of TSCA. There is no basis in this provision or other parts of the law for differentiating between manufacture as a byproduct and purposeful production and including one in a risk evaluation but excluding the other. And in this instance, there's no evidence (and EPA does not claim) that exposure to and release of 1,4-dioxane as a byproduct and impurity are inconsequential from a risk standpoint.[31]

While EPA suggests that it might be more efficient or effective to address byproduct production of 1,4-dioxane in a separate section 6(a) rulemaking for ethoxylated chemicals, this seems far-fetched. If EPA assesses the contribution of these chemicals to 1,4-dioxane water contamination in the current risk evaluation, it will have a sound basis to regulate their production and use under section 6(a) if they are found to present an unreasonable risk of injury.[32] Otherwise, there is no telling when EPA might mitigate water contamination resulting from byproduct production of 1,4-dioxane production. Thus far, EPA has offered no indication when, if ever, it will make a high-priority designation for ethoxylated chemicals and assess their contribution to the presence of 1,4-dioxane in the environment.

We recommend that during problem formulation, EPA add 1,4-dioxane production as a byproduct and impurity to the scope of its risk evaluation.

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[30] Environmental Working Group, HIDDEN CARCINOGEN TAINTS TAP WATER, CONSUMER PRODUCTS NATIONWIDE (September 2017).

[31] Under our interpretation of section 6(b), EPA could not exclude a condition of use from the risk evaluation scope based on low risk in any event.

[32] Section 6(a) does not limit EPA to regulating purposeful production of a chemical subject to a risk evaluation. It can regulate production by other means so long as it has been assessed in that evaluation and found to present an unreasonable risk.

X. BASED ON THE GENERAL PRINCIPLES OUTLINED ABOVE AND OTHER GAPS IN ITS SCOPING DOCUMENTS, EPA SHOULD AUGMENT THESE DOCUMENTS IN SEVERAL SPECIFIC RESPECTS DURING PROBLEM FORMULATION

Applying the general approaches outlined in these comments and in light of several omissions we identified in individual scoping documents, we recommend that EPA bolster those documents during problem formulation as follows:

1-Bromopropane (nPB)

- In our initial comments to EPA, we specifically identified nPB as being imported by companies whose primary business is supplying the cosmetics industry.[33] While the EPA has noted that authorities such as the State of California have included nPB on lists of chemicals banned in cosmetics, the potential for nPB directly or indirectly (through residues remaining from cleaning manufacturing equipment) to be present in cosmetic products is not addressed as a potential use for further assessment.
- As discussed in detail in Part V of these comments, EPA failed to address the ozone depletion potential of nPB.
- While the scoping document includes references to those exposed to nPB from use of the chemical in consumer products, as well as those co-located with dry cleaning facilities utilizing the chemical, it does not clearly identify people who may be further exposed from chemical residuals, such as those wearing clothing cleaned with nPB or their children. This pathway is not discussed, even though the scoping document for PERC includes it from the similar use of PERC in dry cleaning.

Asbestos

- EPA's scoping document claims that public comments were not received on various imported asbestos containing products available in the United States: "Products available from several online retailers and distributers include brake blocks, aftermarket friction products, roof and non-roof coatings, and gaskets, most of which are imported. No public comments were received regarding these uses." However, we submitted detailed comments highlighting all of these items and more, including other building products. [34]
- EPA's failure to include a lengthy list of legacy uses, as further discussed in Part IV of these comments, is especially problematic for asbestos which was extensively sold and distributed and remains widely present and in use in our buildings and cities.
- The recycling of legacy materials, notably asphalt shingles containing asbestos, is a unique and ongoing use of the substance, and in particular is worthy of additional consideration by the EPA, as discussed in our initial comments.[35]

[33] EPA-HQ-OPPT-2016-0741-0027 at PDF Pages 25, 27, 31.
[34] EPA-HQ-OPPT-2016-0736-0064 at PDF Pages 19, 25-27
[35] EPA-HQ-OPPT-2016-0736-0064 at PDF Pages 21-22

- There is evidence that asbestos has been present in significant levels in some talc products as the result of colocation of asbestos and talc deposits, as we discussed in our initial comments.[36] This use and ongoing exposure are not addressed in the scoping document.

- The scoping document fails to look at the risks of exposure to those who are upstream to the process of utilizing asbestos in chlor-alkali processing. This would include miners and packaging workers (who, while likely abroad, are still being exposed as a result of the substance's uses in the US considered by the EPA), as well as transportation workers, first responders, and community members who may be exposed in the shipment and transfer of asbestos to the chlor-alkali facilities.

- The absence in the scoping document of total import volumes for asbestos is troubling because it deprives the public of an understanding of the aggregate quantities of asbestos present in the US. In fact, the Asbestos Disease Awareness Organization, along with the Environmental Working Group, released a statement on September 19 that, based on data from the Department of Commerce and US International Trade Commission, 705 metric tons of raw asbestos were imported in 2016, compared to 343 metric tons in 2015. This significant increase in imports is important information that should be given prominence in the problem formulation document for asbestos.

Carbon Tetrachloride (CTC)

- As discussed in detail in Part V of these comments, EPA failed to address the ozone depletion potential and global warming potential of CTC in its scoping document. This is particularly problematic for CTC, as its use as a feedstock or intermediary was exempted from the Montreal Protocol on the false assumption that CTC production would be phased out. In actuality, CTC production is poised for an increase due to its use in HFO manufacture, as we discussed on our initial comments.[37]

- As discussed in detail in Part III of these comments, EPA failed to describe with any specificity how it will look at aggregate and cumulative exposures. In the CTC scoping document, EPA seems to specifically discredit the need for this consideration. The Agency highlights the fact that some individuals may be exposed to CTC through vapor intrusion of ground sources of CTC into their home, but then states that, ". . . this route is not likely to be significant given the agency's identified conditions of use . . ." Clearly, whether the CTC inhaled by a resident is from the vapor intrusion or from an adhesive product, they face potential health risks from it. The Agency must consider all uses and sources of exposure in the risk evaluation in order to accurately assess the human health risk and fulfill its statutory obligations.

Cyclic Aliphatic Bromides Cluster (HBCD)

- As detailed in Part IV of these comments, EPA must not exclude the ongoing use and disposal from past introduction of HBCD in a variety of products. Significant exposures will continue to occur as products incorporating HBCD move through their lifecycle, and these exposures must be considered in the risk evaluation.

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[36] EPA-HQ-OPPT-2016-0736-0064 at PDF Pages 18-19

[37] EPA-HQ-OPPT-2016-0733-0023 at PDF pages 4-5, 19

N-Methylpyrrolidone (NMP)

- As we documented in our initial comments to the EPA, NMP has been used in the manufacturing of coating for the insides of aluminum spray cans.[38] Even products not including deliberate addition of NMP may therefore be contaminated with NMP, and this exposure pathway should be considered by the Agency.

- As detailed in Part II of these comments, EPA failed to provide specifics on susceptible subpopulations. While the Agency acknowledges that reproductive effects are to be assessed, considering the well-documented reproductive toxicity of NMP, the Agency needs to better detail how the risks to women of childbearing age will be addressed.

Methylene Chloride (MC)

- While the scoping document includes a use categorization for "other consumer products" including novelty "Drinking Bird" items, we identified an additional item,[39] a "Novelty Christmas Bubbling Night Light" labeled as containing MC but not previously included in EPA's "Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: Methylene Chloride." These consumer-oriented uses that are attractive to children illustrate the need to be comprehensive in the determination of "reasonably foreseeable" uses.

XI. EPA MAY NOT PREJUDGE THE ABSENCE OF ADVERSE EFFECTS FOR PARTICULAR END-POINTS AT THE SCOPING STAGE AND SHOULD DEFER SUCH CONCLUSIONS UNTIL THE SYSTEMATIC REVIEW STAGE OF ITS RISK EVALUATION

In some scoping documents, EPA has decided that the subject chemical does not raise concerns for particular endpoints and, therefore, it will not address these end-points in its risk evaluation. Examples are given in the table below where EPA concludes that HBCD, NMP and pigment violet 29 are not genotoxic:

Chemical	Example Text from EPA Scoping Document
HBCD	"Available data suggest that HBCD is not genotoxic. Existing assessments have also concluded, based on genotoxicity information and a limited lifetime study, that HBCD is not carcinogenic (NICNAS, 2012; EINECS, 2008; TemaNord, 2008; OECD, 2007). Unless new information indicates otherwise, EPA does not expect to conduct additional in-depth analysis of genotoxicity or cancer hazards in the risk evaluation of HBCD at this time."[40]
NMP	"NMP is not mutagenic, based on results from bacterial and mammalian *in vitro* tests and *in vivo* systems and is not considered to be carcinogenic (RIVM, 2013; OECD, 2007; WHO, 2001). Unless new information indicates otherwise, EPA does not expect to conduct additional in-depth analysis of genotoxicity and cancer hazards in the NMP risk evaluation."[41]

[38] EPA-HQ-OPPT-2016-0743-0031 at PDF page 18
[39] https://www.amazon.com/Bubble-Nightlight-Novelty-Christmas-Bubbling/dp/B00PV61HXC/
[40] EPA, *Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster, June 2017, at.* 36
[41] EPA, *Scope of the Risk Evaluation for N-Methylpyrrolidone,* June 2017, *at* 36

Pigment violet 29	"Testing for carcinogenicity of Pigment Violet 29 has not been conducted. However, negative genotoxicity results, structure-activity considerations and the expectation of negligible absorption and uptake of Pigment Violet 29 (based on very low solubility), indicate carcinogenicity of Pigment Violet 29 is unlikely. Unless new information indicates otherwise, EPA does not expect to conduct additional, in-depth analyses of genotoxicity and cancer hazards in the risk evaluation of Pigment Violet 29."[42]

EPA cannot reach such definitive conclusions at the scoping stage. The required course under the law is to proceed with a systematic review of the relevant data (a process that EPA strongly endorses) and withhold any conclusions about particular end-points until this review is complete.

In the case of HBCD, for example, a more thorough review would reveal two recent studies indicating carcinogenic potential. One suggests that HBCD could "enhance progression of prostate cancer by modulating growth and migration of LNCaP prostate cells,"[43] and the other concludes the genotoxicity of HBCD is dose-dependent and related to DNA repair.[44] These new studies are examples of the need for EPA to assure that it has fully considered all the available data through the systematic review process in order to avoid premature and possibly incorrect decisions to drop particular end-points at the scoping stage.

XII. PROBLEM FORMULATIONS SHOULD HIGHLIGHT ASPECTS OF USE AND EXPOSURE WHERE AVAILABLE INFORMATION IS INSUFFICIENT AND REQUEST OR REQUIRE SUBMISSION OF THIS INFORMATION BY INDUSTRY

Our own research on the 10 chemicals and the scoping documents themselves confirm that there are significant gaps in the use and exposure information available to EPA and that they will weaken the quality of EPA's risk evaluations unless filled. Although the timeframe for completing risk evaluations is compressed, there is still a window for augmenting the information-base used to conduct them. To take advantage of this opportunity, EPA should include in each problem formulation document a description of information on use and exposure that is lacking and a request that industry and other interested parties submit or obtain that information as expeditiously as possible.

EPA should also signal its readiness to use its mandatory information collection authorities under TSCA to fill data-gaps where voluntary submissions are not timely or adequate. The LCSA expands these authorities and streamlines the process for exercising them, removing the barriers to information development that hamstrung EPA under the old law. For example, section 4 now authorizes EPA to issue orders where necessary to "perform a risk evaluation." Such orders can be used to require industry to develop new information on the frequency, levels and duration of exposure for a chemical's conditions of use. Alternatively, EPA can use its subpoena authority under section 11 to obtain such information that already exists but has not been provided to EPA. EPA should specify in the problem formulation document its roadmap and timetable for filling data gaps using these authorities.

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[42] EPA, *Scope of the Risk Evaluation for Pigment Violet 29*, June 2017, at 29.

[43] Seung-Hee Kim, et al, 2016. Influence of hexabromocyclododecane and 4-nonylphenol on the regulation of cell growth, apoptosis and migration in prostatic cancer cells. Toxicology in Vitro. 32:240-247. April 2016.

[44] Rui Jing Li, et al. Hexabromocyclododecane-induced Genotoxicity in Cultured Human Breast Cells through DNA Damage. Letter to Editor. Biomedical and Environmental Sciences. 30(4): 296-300.

Where the database available for a risk evaluation is incomplete, it is critically important that EPA not equate the absence of data with the absence of risk. For example, if EPA lacks data to assess a chemical's carcinogenicity, its risk evaluation needs to clearly state that cancer risk has not been addressed, that the chemical may or may not present such a risk, and that this end-point is outside the scope of its evaluation because of the absence of data. EPA should make the same disclaimers for conditions of use that cannot be adequately characterized, even by using default assumptions or extrapolation methods, because basic information about the nature of the use and scope and extent of exposure is unavailable.

XIII. EPA NEEDS TO LIMIT REDACTION FROM SCOPING AND PROBLEM FORMULATION DOCUMENTS OF CRITICAL INFORMATION CLAIMED CBI SO THAT TRANSPARENCY AND PUBLIC PARTICIPATION IN THE RISK EVALUATION PROCESS ARE NOT IMPAIRED

The scoping documents omit critical exposure and use information that has been claimed as confidential business information (CBI) that must be withheld from disclosure under TSCA. In some cases, the information is as basic as the total volume of the chemical manufactured and imported in the US. For example, the scoping documents fail to provide total manufacture/import volumes for asbestos, HBCD and pigment violet 29. Not only is this information obtainable in the public domain but it is fundamental to public understanding of the risks posed by these chemicals and, therefore, to informed public participation in the risk evaluation process.[45]

During problem formulation, EPA should make a concerted effort to limit the redaction of CBI-claimed production, use and exposure data that are essential for the transparency of the risk evaluation process. Several tools can be used for this purpose.

First, section 14(b)(3) of TSCA declares that "information not protected from disclosure" includes:

> "any general information describing the manufacturing volumes, expressed as specific aggregated volumes or . . . expressed in ranges."
>
> "a general description of a process used in the manufacture or processing and industrial, commercial or consumer functions and uses of a chemical, substance, mixture or article containing a chemical substance or mixture . . ."

This provision compels the disclosure of much of the information in scoping documents claimed CBI.

Alternatively, section 14(d)(7) provides that the Administrator may disclose information otherwise warranting CBI protection if he or she "determines that disclosure is relevant in a proceeding under this Act." The risk evaluations that EPA is conducting on the 10 chemicals under section 6(b)(2)(A) of TSCA represent a "proceeding" under TSCA. Information submitted by industry on the 10 chemicals is plainly "relevant" to these evaluations because it will inform how EPA assesses exposures and related risks

[45] For asbestos, SCHF and Environmental Health Strategy Center were able to use US government data accessible through the Panjiva database to determine annual asbestos imports over an extended period. As noted above, a more recent analysis of import data by the Asbestos Disease Awareness Organization shows that asbestos imports doubled in 2016, a startling finding that should be central to EPA's risk evaluation because of its implications for exposure to asbestos in the US.

associated with manufacture, processing and downstream commercial and consumer use. Thus, EPA can and should decide to disclose all information on the 10 chemicals notwithstanding any CBI claims.

Finally, to the extent these grounds for disclosure do not apply, EPA should use its authority under section 14(f)(1)(C) to require immediate substantiation of CBI claims for information for which "disclosure would be important to assist the Administrator in conducting risk evaluations . . . under section 6." This provision should be applied broadly to accomplish disclosure of all information that would be of value to the public in commenting on risk evaluations.

CONCLUSION

Our groups appreciate the opportunity to comment on the 10 scoping documents and look forward to continued dialogue with the Agency as it develops problem formulation documents and proceeds with risk evaluations on the 10 chemicals.

If you have any questions, please contact SCHF counsel, Bob Sussman, at bobsussman1@comcast.net or 202-716-0118.

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High discordance in development and organ site distribution of tumors in rats and mice in NTP two-year inhalation studies

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Abstract

The National Toxicology Program (NTP) reports 60 two-year inhalation studies in both mice and rats on single agents or closely related agents. "Cadmium and cadmium compounds" and "diesel exhaust particulates" were omitted from this analysis due to lack of results regarding a particular compound. No Ames test data were available for antimony trioxide, nickel sulfate hexahydrate, and indium phosphide. For antimony trioxide, a comet assay was used as a surrogate for the Ames test. To eliminate selection bias, all positive Ames assay test results and any statistically significant increase in lung tumor incidence over background in an NTP two-year inhalation study were accepted at face value. For the 58 compounds tested via inhalation by NTP, there is a high degree of discordance between mice and rats in the susceptibility to develop lung tumors. The causation of tumors at anatomical sites outside the lung via the inhalation route is also discordant in mice and rats, for example, 11/58 (19%) of agents tested in the NTP inhalation studies using mice and rats were negative in the Ames assay test and showed lung tumors in mice only. The ability to form lung tumors in mice in the absence of genotoxicity demonstrates that other mechanisms, for example, cytotoxicity followed by reparative cellular proliferation, might be involved. Mouse and rat data are discordant regarding the ability to induce tumors at organ sites outside the lungs—0/58 as compared with 16/58, respectively. Mice and rats display distinctly different patterns of both lung tumor development and development of tumors outside the lungs.

Keywords

NTP, rats, mice, lung tumors, discordance, inhalation

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Introduction

The National Toxicology Program (NTP) is a branch of the United States Department of Health and Human Services. One of NTP's major current programs is "The Toxicology in the 21st Century: The Role of the National Toxicology Progra7m."[1] On their website, NTP describes this program as follows:

> The Role of the National Toxicology Program is to support the evolution of toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations. The intent of NTP vision is to expand the scientific basis for making public health decisions on the potential toxicity of environmental agents.

One of the major "disease-specific models" employed by NTP is the 2-year rodent inhalation bioassay.

The NTP National Institute of Environmental Health Science (NIEHS) website references 60 two-year inhalation studies conducted in both rats and mice on single agents or closely related agents.[2] Two of the 60 inhalation

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Table 1. Summary analysis of the 58 different agents tested in two-year inhalation studies conducted on both rats and mice by the NTP.

(a)

Species	Fraction (%) of 58 agents causing lung tumors only[a]	Fraction of 58 agents causing non-lung tumors only[b]	Fraction of Ames assay test negative agents causing lung tumors only[c]	Fraction of Ames assay test negative agents causing non-lung tumors only[d]	Fraction of Ames assay test positive agents causing lung tumors only[e]	Fraction of Ames assay test positive agents causing non-lung tumors only[f]	Fraction of agents causing non-lung tumors in one species only[g]
Rats	7/58 (12.1%)	34/58 (58.6%)	3/58 (5.2%)	25/58 (43.1%)	1/58 (1.7%)	14/58 (24.1%)	16/58 (27.6%)
Mice	15/58 (25.9%)	10/58 (17.2%)	11/58 (19.0%)	10/58 (17.2%)	6/58 (10.3%)	1/58 (17.2%)	0/58

(b)

Ames assay test result	Fraction of agents causing lung tumors in both rats and mice[h]	Fraction of agents not causing lung tumors in either rats or mice[i]
Positive	9/58 (15.5%)	1/58 (1.7%)
Negative	5/58 (8.6%)	22/58 (37.9%)

(c)

Species	Fraction of agents not causing tumors at any site[j]	Fraction of agents causing tumors at any site[k]
Rats	9/58 (15.5%)	49/58 (84.5%)
Mice	17/58 (29.3%)	41/58 (70.7%)

NTP: National Toxicology Program.
[a]Borderline at 95% significant difference between rats and mice at $p\text{-value}_1 = 0.0588$; $p\text{-value}_2 = 0.0549$.
[b]Statistically significant difference between rats and mice at $p\text{-value}_1 < 0.0001$; $p\text{-value}_2 < 0.0001$.
[c]Statistically significant difference between rats and mice at $p\text{-value}_1 = 0.0226$; $p\text{-value}_2 = 0.0198$.
[d]Statistically significant difference between rats and mice at $p\text{-value}_1 = 0.0024$; $p\text{-value}_2 = 0.0016$.
[e]Statistically significant difference between rats and mice at $p\text{-value}_1 = 0.0512$; $p\text{-value}_2 = 0.0477$.
[f]Statistically significant difference between rats and mice at $p\text{-value}_1 = 0.0003$; $p\text{-value}_2 < 0.0001$.
[g]Statistically significant difference between rats and mice at $p\text{-value}_1 = < 0.0001$; $p\text{-value}_2 < 0.0001$.
[h]No significant difference in Ames assay positive and Ames assay negative agents at $p\text{-value}_1 = 0.2543$; $p\text{-value}_2 = 0.2501$.
[i]Statistically significant difference in Ames assay positive and Ames assay negative agents at $p\text{-value}_1 < 0.0001$; $p\text{-value}_2 < 0.0001$.
[j]No significant difference between rats and mice at $p\text{-value}_1 = 0.0751$; $p\text{-value}_2 = 0.0703$.
[k]No significant difference between rats and mice at $p\text{-value}_1 = 0.0751$; $p\text{-value}_2 = 0.0703$.

studies were conducted on "cadmium and cadmium compounds"[3] and on "diesel exhaust particulates."[4] These two studies were omitted from this analysis due to lack of results regarding a particular compound. In each of the 58 two-year rodent inhalation studies analyzed herein, the mouse strain $B6C3F_1$ was used. In 55/58 studies, the rat strain employed was F344/N. Wistar Han rats were used for the inhalation studies on Trim® VX and antimony trioxide. Osborne-Mendel rats were used for the inhalation study of allyl glycidyl ether. For three compounds, no Ames assay test data were available: antimony trioxide, nickel sulfate hexahydrate, and indium phosphide. Antimony trioxide had a positive comet assay, so that result was considered equivalent to a positive Ames assay test.

In the vast majority of cases where a benign adenoma in the rodent lung was seen, a malignant bronchioloalveolar carcinoma was also detected. Since benign adenomas in rodent lungs are precursors to the development of malignant bronchioloalveolar carcinomas,[5] the practice of considering the tumor types as interchangeable for counting purposes was followed. In a limited number of cases, the only anatomical site outside the lung that developed tumors was the nasal passages. In this analysis, the nasal passages are considered separately from the lungs, but it could also be argued that tumorigenicity of the lungs and nasal passages could be combined although there are microanatomical and physiological differences between the two anatomic locations.[6]

Table 2. 11/58 Total NTP inhalation studies conducted in rats and mice are negative in the Ames assay and had lung tumors for mice only.

Chemical	Reference	Ames assay test	Clastogen	Physicochemical characteristics[a]	Route of exposure	Lung tumors	Nonneoplastic findings
Nitrobenzene CAS No. 98-95-3	RoC 13th edition	Negative	Positive in chromosome aberrations in humans. SCEs negative in vitro	Slightly soluble in water, soluble in organic solvents. Log $p = 1.85$	Inhalation	Positive in male mice; negative in female mice and rats	Incidences of alveolar/bronchiolar hyperplasia (a presumed preneoplastic lesion was significantly increased in male mice at the mid and high doses and in female mice at the mid dose)
Trichloro-ethylene CAS No. 79-01-6	RoC 13th edition	Negative	Probably negative, but did cause SCE	Slightly soluble in water, soluble in ethanol, acetone, diethyl ether, and chloroform, and miscible in oil. Log $p = 2.61$	Inhalation	Clear evidence in male and female mice; negative in rats	
Vinylidene chloride CAS No. 75-35-4	NTP TR 582, August, 2015	Negative	Negative in micronucleus	Clear volatile liquid, insoluble in water but miscible with most organic solvents. Log $p = 2.13$	Inhalation	Incidence of alveolar/ bronchiolar carcinoma significantly increased in 12.5 ppm female mice; negative in male mice and in rats	Respiratory epithelium, hyperplasia
1-Bromopropane CAS No. 106-94-5	NTP TR 564, August 2011	Negative	Positive in chromosome aberrations	Slightly soluble in water, soluble in most organic solvents. Log $p = 2.10$	Inhalation	Clear evidence in female mice; No evidence in male mice and rats	Bronchiole, regeneration
Cumene CAS No. 98-82-8	NTP TR 542, February 2009	Negative	Probably negative but did cause small increase micronucleus	Alkylated benzene volatile at room temperature. Log $p = 3.66$	Inhalation	Clear evidence in male and female mice; negative in rats	Bronchiolar hyperplasia and alveolar epithelial bronchiolar metaplasia significantly increased in mice of both sexes
Divinylbenzene-HP CAS No. 1321-74-0	NTP TR 534, Nov 2006	Negative	Negative in micronucleus	Insoluble in water and soluble in methanol and ether. Log $p = 3.8$	Inhalation	Equivocal evidence of carcinogenic activity in female mice; negative male mice, male and female rats	Bronchiolar, hyperplasia, atypical, alveolar epithelium, hyperplasia
Naphthalene CAS No. 91-20-3	NTP TR 500, December 2000; NTP TR edition	Negative	Positive in chromosome aberrations and SCE	Not soluble in water, soluble in organic solvents. Log $p = 3.3$	Inhalation	Significantly increased incidence of benign lung tumors (adenoma) in female B6C3F1 mice	Nonneoplastic lesions attributed to naphthalene exposure were observed in the nose and lungs of mice of both sexes. In the nose, naphthalene exposure was associated with an increase in the incidence and severity of chronic inflammation, metaplasia of the olfactory epithelium, and hyperplasia of respiratory epithelium. Chronic inflammation in the lung was associated with chemical exposure
Chloroprene CAS No. 126-99-8	NTP TR 467, September 1998	Negative	Negative in chromosome aberrations, SCEs, or micronucleus	Practically insoluble in water, soluble in alcohol, and miscible with acetone, benzene, and ethyl ether. Log $p = 2.53$	Inhalation	Positive in male and female mice; negative rats	Increased incidences of bronchiolar hyperplasia and histiocytic cell infiltration in the lung

(continued)

Table 2. (continued)

Chemical	Reference	Ames assay test	Clastogen	Physicochemical characteristics[a]	Route of exposure	Lung tumors	Nonneoplastic findings
Ethylbenzene CAS No. 100-41-4	NTP TR 466, January 1999	Negative	Negative for SCE or chromosome aberrations	Practically insoluble in water but soluble in most organic solvents. Log $p = 3.15$	Inhalation	Some evidence of carcinogenic activity in male mice; negative in female mice and rats	Alveolar epithelial metaplasia
Nitromethane CAS No. 75-52-5	NTP TR 461, February 1997	Negative	Negative in chromosome aberrations, SCE, and micronucleus	Soluble in water, alcohol, ether, acetone, and dimethylformamide. Log $p = 0.17$	Inhalation	Positive in male and female mice. Negative in rats	Hyaline degeneration of respiratory epithelium
Isoprene CAS No. 78-79-5	NTP TR 486, July 1999	Negative	Negative for SCE or chromosome aberrations in vitro. Positive in vivo in mice for SCE and micronucleus	Log $p = 2.42$	Inhalation	Positive in male and female mice; negative in rats	Alveolar epithelial hyperplasia

NTP: National Toxicology Program.
Ten of the 11 chemicals in this table are insoluble or slightly soluble in water, soluble in organic solvents, and have hydrophobic octanol–water partition coefficients of 0.17, 1.85, 2.10, 2.13, 2.42, 2.53, 2.61, 3.15, 3.30, 3.66, and 3.80. These chemicals induce hyperplasia in the airways of mice.
[a]All physicochemical values are from the Hazardous Substances Database unless otherwise designated.

Table 3. 3/58 Total NTP inhalation studies conducted in rats and mice that are negative in the Ames assay test and show lung tumors for rats only.

Chemical	References	Ames assay test	Clastogen	Physicochemical characteristics[a]	Route of exposure	Lung tumors	Nonneoplastic findings
Gallium arsenide CAS No. 1303-00-0	NTP TR 492 September 2000	Negative	Negative micronucleus assay	Insoluble in water. Particulate aerosols with MMAD 1 μm	Inhalation	No evidence in male rats; *clear evidence in female rats*; no evidence in male and female mice	Atypical epithelial hyperplasia, chronic active inflammation, metaplasia in lung
Nickel subsulfide CAS No. 12035-72-2	NTP TR 453, July 1996	Negative	Positive in chromosome aberrations and micronucleus	Black powder, insoluble in water, soluble in acid. MMAD 2.0–2.2 μm	Inhalation	*Clear evidence in male and female rats*; no evidence in male or female mice	Chronic active inflammation, focal alveolar hyperplasia
Talc containing no asbestos fibers CAS No. 14807-96-6	NTP TR 421, September 1993	Negative	Negative	Insoluble in water. Finely powdered hydrous magnesium silicate, MMAD 2.7–3.2 μm for rats, and MMAD 3.3 μm for mice	Inhalation	*Clear evidence in female rats*; no evidence in male rats, or male or female mice	Chronic granulomatous inflammation, alveolar epithelial hyperplasia, epithelial squamous metaplasia

NTP: National Toxicology Program; MMAD: mass mean aerodynamic diameter.
The three agents in this table contain metals, consist of particles, and are not soluble in water.
[a]All physicochemical values are from the Hazardous Substances Database unless otherwise designated.

Table 4. 5/58 Total NTP inhalation studies conducted in rats and mice are negative in the Ames assay test and show lung tumors in both rats and mice.

Chemical	References	Ames assay test	Clastogen	Physicochemical characteristics	Route of exposure	Lung tumors	Nonneoplastic findings
Trim VX	NTP 591, Scheduled Peer Review Date: February 16, 2016	Negative	Negative in micronucleus	Forms a chemical emulsion with water. Metalworking fluid used as a lubricant and coolant liquid	Inhalation	There was *equivocal evidence of carcinogenic activity* of Trim VX in male Wistar Han rats based on the combined occurrences of alveolar/bronchiolar adenoma or carcinoma of the lung. There was *equivocal evidence of carcinogenic activity* of Trim VX in female Wistar Han rats based on the occurrences of alveolar/bronchiolar adenoma of the lung. There was *clear evidence of carcinogenic activity* of Trim VX in male B6C3F1/N mice based on the increased combined incidences of alveolar/bronchiolar adenoma or carcinoma of the lung. There was *clear evidence of carcinogenic activity* of Trim VX in female B6C3F1/N mice based on the increased combined incidences of alveolar/bronchiolar adenoma or carcinoma (primarily carcinoma) of the lung	*Lung male mice:* alveolar/bronchiolar epithelium, hyperplasia (3/50, 7/50, 15/49, 50/50); infiltration cellular, histiocyte (5/50, 9/50, 15/49, 49/50); inflammation, chronic (5/50, 12/50, 16/49, 50/50); alveolar epithelium, hyperplasia (3/50, 3/50, 7/49, 47/50); fibrosis (0/50, 2/50, 5/49, 45/50) *Lung female mice:* alveolar/bronchiolar epithelium, hyperplasia (0/50, 3/50, 8/50, 45/50); infiltration cellular, histiocyte (1/50, 4/50, 15/50, 48/50); inflammation, chronic (1/50, 6/50, 26/50, 47/50); alveolar epithelium, hyperplasia (0/50, 0/50, 2/50, 43/50); fibrosis (0/50, 0/50, 2/50, 42/50)
Vanadium pentoxide CAS No. 1314-62-1	NTP TR 507, December 2002	Negative	Negative in micronucleus	Dosed as a particulate aerosol; an odorless, yellow to reddish brown orthorhombic crystal; insoluble in alcohol; is slightly soluble in water with a water solubility of 1 g/125 mL, and is soluble in concentrated acid, alkalies (forming vanadates), and acetone.	Inhalation	Under the conditions of this 2-year inhalation study, there was some evidence of carcinogenic activity[a] of vanadium pentoxide in male F344/N rats and equivocal evidence of carcinogenic activity of vanadium pentoxide in female F344/N rats based on the occurrence of alveolar/bronchiolar neoplasms. There was clear evidence of carcinogenic activity of vanadium pentoxide in male and female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms	Exposure to vanadium pentoxide caused a spectrum of nonneoplastic lesions in the respiratory tract (nose, larynx, and lung) including alveolar and bronchiolar epithelial hyperplasia, inflammation, fibrosis, and alveolar histiocytosis of the lung in male and female rats and mice and an unusual squamous metaplasia of the lung in male and female rats. Hyperplasia of the bronchial lymph node occurred in female mice

(continued)

Table 4. (continued)

Chemical	References	Ames assay test	Clastogen	Physicochemical characteristics	Route of exposure	Lung tumors	Nonneoplastic findings
Cobalt sulfate CAS No. 10124-43-3 cobalt sulfate heptahydrate	NTP TR 471, August 1998	Negative	Negative	Cobalt sulfate is a reddish, crystalline, water-soluble powder (Smith and Carson, 1981).[7]	Inhalation	Some evidence in male rats; clear evidence in female rats, male mice, female mice	Exposure to cobalt sulfate heptahydrate caused a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice
Molybdenum trioxide CAS No. 1313-27-5	NTP TR 462, April 1997	Negative	Negative	Molybdenum trioxide is a white or slightly yellow to slightly bluish powder with a boiling point of 1155°C, a melting point of 795°C, and a specific gravity of 4.50 at 19.5°C. It is soluble in water (0.49 g/L at 28°C), concentrated mineral acids, and solutions of alkali hydroxides, ammonia, and potassium bitartrate. Its vapor pressure is less than 103 mm Hg at 600°C (Merck Index, 1989)	Inhalation	Equivocal evidence in male rats, some evidence of carcinogenic activity in male mice, some evidence in female mice	Exposure of male and female rats to molybdenum trioxide by inhalation resulted in increased incidences of chronic alveolar inflammation, hyaline degeneration of the respiratory epithelium, hyaline degeneration of the olfactory epithelium (females), and squamous metaplasia of the epiglottis; exposure of male and female mice to molybdenum trioxide by inhalation resulted in increased incidences of metaplasia of the alveolar epithelium, histiocyte cellular infiltration (males), hyaline degeneration of the respiratory epithelium, hyaline degeneration of the olfactory epithelium (females), squamous metaplasia of the epiglottis, and hyperplasia of the larynx

(continued)

Table 4. (continued)

Chemical	References	Ames assay test	Clastogen	Physicochemical characteristics	Route of exposure	Lung tumors	Nonneoplastic findings
Nickel oxide CAS No. 1313-99-1	NTP TR 451, July 1996	Negative	Negative in micronucleus; negative in chromosome aberrations	Nickel oxide (high temperature green nickel oxide, oxidized at 870–900°C and heated to 1350°C; Boldt, 1967)[8] is an olive gray powder with a melting point of 2090°C and a density of 7.45 g/cm^3. It is insoluble in water and soluble in acids (Merck Index, 1989).[9] The mean values for the mass median aerodynamic diameter at each exposure concentration of nickel oxide used in these 2-year studies ranged from 2.2 to 2.6/μm. The nickel oxide used in these studies is only one form of nickel oxide within a larger family of "oxidic" nickels	Inhalation	Some evidence in male and female rats; equivocal evidence mice; negative in male mice	Exposure of rats to nickel oxide by inhalation for 2 years resulted in inflammation and pigmentation in the lung, lymphoid hyperplasia and pigmentation in the bronchial lymph nodes, and hyperplasia of the adrenal medulla (females). Exposure of mice to nickel oxide by inhalation for 2 years resulted in bronchialization, proteinosis, inflammation, and pigmentation in the lung and lymphoid hyperplasia and pigmentation in the bronchial lymph nodes

NTP: National Toxicology Program.
Four of the five agents in this table are powdered metals. One of the five, Trim VX is a water-soluble oil that forms a chemical emulsion. Each of these five agents caused inflammation and hyperplasia in the lungs.
[a]All physicochemical values are from the Hazardous Substances Database unless otherwise designated.

Table 5. 9/58 Total NTP inhalation studies conducted in rats and mice are positive in the Ames assay test and show lung tumors in both rats and mice.

Chemical	References	Ames assay test	Clastogen	Physicochemical characteristics	Route of exposure	Lung tumors	Nonneoplastic findings
Antimony trioxide CAS No. 1309-64-4	NTP TR 590 (February, 2016)	Positive Comet Assay in mouse lung tissue samples	Positive micronucleus	Slightly soluble in water, dilute sulfuric acid, and dilute nitric acid	Inhalation	*Some evidence of carcinogenic activity* of antimony trioxide in male and female Wistar Han rats based on increased combined incidences of alveolar/bronchiolar adenoma or carcinoma in the lung. Clear evidence in male and female mice	Antimony trioxide dust and fumes have been shown to cause irritation of the respiratory tract and mucous membranes
Cobalt metal CAS No. 7440-48-4	TR 581, December 2014	Positive	Negative in micronucleus	Soluble in dilute acids	Inhalation	Clear evidence in male rats, female rats, male mice, female mice	Inflammation and hyperplasia in all four rodent types
Isobutyl nitrite CAS No. 542-56-3	NTP TR 448, July 1996	Positive	Positive in SCE and chromosome aberrations	Slightly soluble in water	Inhalation	There was clear evidence of carcinogenic activity of isobutyl nitrite in male and female F344/N rats based on the increased incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined). There was some evidence of carcinogenic activity of isobutyl nitrite in male and female B6C3F_1 mice based on the increased incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) in males and females	Bronchiolar and alveolar hyperplasia
Tetranitromethane CAS No. 509-14-8	NTP TR 386, March 1990	Positive	Positive chromosome aberrations and SCEs	Log K_{ow}-2.05. Soluble in ethanol, ether, and CCl_4. Soluble in water. Freely soluble in alcoholic KOH	Inhalation	Clear evidence of carcinogenic activity[a] of tetranitromethane for male and female F344/N rats and male and female B6C3F1 mice, based on increased incidences of alveolarbronchiolar neoplasms in both species and squamous cell carcinomas of the lung in rats	Alveolar hyperplasia. Hyperplastic and squamous metaplasia or respiratory epithelium

(continued)

Table 5. (continued)

Chemical	References	Ames assay test	Clastogen	Physicochemical characteristics	Route of exposure	Lung tumors	Nonneoplastic findings
Allyl glycidyl ether CAS No. 106-92-3	NTP TR 376, January 1990	Positive	Positive in SCE and chromosome aberrations	Soluble in water	Inhalation	Equivocal evidence of carcinogenic activity in male Osborne-Mendel rats, no evidence in female rats, some evidence in male mice, equivocal evidence in female mice	Male mice had dysplasia, both sexes had focal basal cell hyperplasia of respiratory epithelium in nasal passages
Bromoethane (ethyl bromide) CAS No. 74-96-4	NTP TR 363, October 1989	Positive	Positive for SCEs and negative for chromosome aberrations	Log K_{ow} 1.61. Soluble in water, alcohol, ether, chloroform, and organic solvents	Inhalation	Some evidence in male rats, equivocal evidence in female rats, equivocal evidence in male mice. Negative in female mice	Alveolar and nasal epithelial hyperplasia
1,2-Dibromoethane CAS No. 106-93-4	TR-210, March 1982	Positive–direct acting mutagen	Positive in SCE and DNA binding	Log K_{ow} 1.61. Soluble in water and most organic solvents	Inhalation	Positive in male and female mice and in female rats; negative in male rats	Epithelial hyperplasia, squamous metaplasia, and suppurative inflammation
Chromium hexavalent compounds CAS No. 18540-29-9	TR-546 (May, 2007), 13th RoC	Positive	Positive	Not applicable	Inhalation	Exposure to chromium(VI) compounds (calcium chromate, chromium trioxide, or sodium dichromate) via inhalation or intratracheal or intrabronchial implantation caused benign and/or malignant lung tumors in rats and/or mice	
Bis(chloromethyl) ether and technical grade chloromethyl methyl ether CAS Nos. 542-88-1 and 107-30-2	12th RoC	Positive	Positive	K_{ow} 1.04. Soluble in water and many organic solvents	Inhalation	Exposure to BCME by inhalation caused lung tumors in rats and mice	

NTP: National Toxicology Program.
[a]All physicochemical values are from the Hazardous Substances Database unless otherwise designated.

Table 6. 6/58 Total NTP inhalation studies conducted in rats and mice are positive in the Ames assay test and show lung tumors in mice only.

Chemical	References	Ames assay test	Clastogen	Physicochemical characteristics	Route of exposure	Lung tumors	Nonneoplastic findings
CIMSTAR 3800	NTP TR 586, September 2015	Direct mutagen in *Escherichia coli* but negative in TA98 and TA100; weakly positive	Negative in micronucleus in vivo	Semi-synthetic metal-working fluid, complex mixture of chemicals	Inhalation	Some evidence of carcinogenic activity in *female mice*. Negative in male mice and rats	Increased bronchiole hyperplasia, alveolar epithelium hyperplasia, histiocytic cellular infiltration
Ozone (CAS No. 10028-15-6)	NTP TR 440	Positive—direct mutagen in TA102	Negative in Chinese hamster ovary cells	Calculated Log $p = -0.87$	Inhalation	There was equivocal evidence of carcinogenic activity of ozone in *male* B6C3F$_1$ *mice* based on increased incidences of alveolar/bronchiolar adenoma or carcinoma. There was some evidence of carcinogenic activity of ozone in *female* B6C3F$_1$ *mice* based on increased incidences of alveolar/bronchiolar adenoma or carcinoma. Negative in rats	Increased incidences of metaplasia occurred in the nose and lung of mice exposed to 0.5 or 1.0 ppm ozone. The metaplasia in the nose consisted of increased thickening and extension of the squamous epithelium in the anterior portion of the nasal passage. The metaplasia in the lung consisted of extension of the bronchial epithelium into the alveoli of the centriacinar region
1,3-Butadiene CAS No. 106-99-0	NTP TR 434, May 1993	Metabolites are direct acting mutagens in TA100, 1535 with S9 activation	Positive in chromosome aberrations	Log $p = 1.99$. Soluble in water and some organic solvents	Inhalation	Clear evidence in male and female mice; negative in rats	Alveolar epithelial hyperplasia in mice
Chloroethane (ethyl chloride) CAS No. 75-00-3	NTP TR 346, October 1989	Positive to TA1535 without S9 activating agent	Positive chromosomal aberrations	Log $p = 1.43$. Chloroethane is 0.57% (w/v) soluble in water at 20°C, 48% soluble in ethyl alcohol at 21°C, and miscible with ethyl ether	Inhalation	Positive in *male mice*; negative in female mice and rats	None
Dichloromethane (methylene chloride) CAS No. 75-09-2	NTP TR 306, January 1986	Positive—direct acting Ames assay mutagen TA98 and TA100	Positive in chromosomal aberrations	Log $p = 1.25$. Soluble in water.	Inhalation	Clear evidence of carcinogenicity in male and female mice; negative in rats	Female rats showed squamous metaplasia of nasal cavity in high-dose group
1,2-Dibromo-3-chloropropane CAS No. 96-12-8	NTP TR 206, March 1982	Positive to TA1535 without S9	Positive in mouse local lymph node assay	Log $p = 2.96$. Soluble in miscellaneous aliphatic and aromatic hydrocarbons; soluble in water	Inhalation	Positive in male and female mice; negative in rats	Multifocal epithelial hyperplasia

NTP: National Toxicology Program.
All six of the chemicals that are positive in the Ames assay test and that cause lung tumors in mice only are direct acting Ames assay mutagens that do not require metabolic activation by hepatic S9 fraction.
[a]All physicochemical values are from the Hazardous Substances Database unless otherwise designated.

NTP considers results from the Ames assay test to be very important in its deliberations as illustrated by the following statement from a recent Report on Carcinogens.[10]

> DNA reactivity combined with *Salmonella* mutagenicity is highly correlated with induction of carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites.[11] A positive response in the *Salmonella* test was shown to be the most predictive in vitro indicator for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens).[12,13] Additionally, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone...

To eliminate the introduction of selection bias into this analysis, all positive Ames assay *Salmonella* bacterial mutagenicity test results reported in the literature and any statistically significant increase in lung tumor incidence over background in an NTP two-year inhalation study were accepted at face value.

Statistical methods

The following tests were applied to assess the statistical significance of the differences in proportions.[14]

Pooled test:

$$H_0 : p_1 - p_2 = 0$$

$$z = \frac{(\hat{p}_1 - \hat{p}_2)}{\hat{p}(1-\hat{p})\frac{1}{n_1} + \frac{1}{n_2}}$$

$$\hat{p} = \frac{x_1 + x_2}{n_1 + n_2}$$

Unpooled test:

$$H_0 : p_1 - p_2 = 0$$

$$z = \frac{(\hat{p}_1 - \hat{p}_2)}{\frac{\hat{p}_1(1-\hat{p}_1)}{n_1} + \frac{\hat{p}_2(1-\hat{p}_2)}{n_2}}$$

Results

Table 1 presents a summary of the proportions of the 58 compounds tested by NTP in both rats and mice in two-year inhalation studies. The fraction of agents that only cause lung tumors was 7/58 (12.1%) in rats and 15/58 (25.9%) in mice. At 95% confidence, the difference in these proportions was borderline significant at $p\text{-value}_1 = 0.0588$ (pooled test) and $p\text{-value}_2 = 0.0549$ (unpooled test). The fraction of agents that only cause tumors outside the lung was 34/58 (58.6%) in rats and 10/58 (17.2%) in mice ($p\text{-value}_1 < 0.0001$; $p\text{-value}_2 < 0.0001$). The fraction of agents that are both negative in the Ames assay test and only cause lung tumors was 3/58 (5.2%) in rats and 11/58 (19.0%) in mice ($p\text{-value}_1 = 0.0226$; $p\text{-value}_2 = 0.0198$). The fraction of agents that are both positive in the Ames assay test and

Table 7. 1/58 Total NTP inhalation studies conducted in rats and mice are positive in the Ames assay test and show lung tumors in rats only.

Chemical	Date	Ames assay test	Clastogen	Physicochemical characteristics[a]	Route of exposure	Lung tumors	Nonneoplastic findings
1,2-epoxybutane CAS No. 106-88-7	March 1988	Positive direct-acting alkylating agent	Positive in SCE and chromosome aberrations	Colorless liquid, soluble in water, ethanol, and most organic solvents	Inhalation	Clear evidence in male rats; no evidence in female rats, or male or female mice. The highest exposure concentration selected for the 2-year studies in rats was 400 ppm. The highest concentration selected for the 2-year studies in mice was 100 ppm because the nasal lesions seen at 200 and 400 ppm were considered to be potentially life-threatening	1,2-Epoxybutane exposure was associated with adenomatous hyperplasia and inflammatory lesions of the nasal cavity in rats and inflammatory lesions of the nasal cavity in mice

NTP: National Toxicology Program.
The negative result in mice is confounded by the maximum dose in mice being ¼ the maximum dose in rats.
[a]All physicochemical values are from the Hazardous Substances Database unless otherwise designated.

Table 8. 22/58 Total NTP inhalation studies conducted in rats and mice are negative in the Ames assay test and show lung tumors in neither rats nor mice.

Chemical	Date	Ames assay test	Clastogen	Physicochemical characteristics[a]	Route of exposure	Lung tumors	Nonneoplastic findings
Diethylamine CAS No. 109-89-7	NTP TR 566, October 2011	Negative	Negative in micronucleus	Log $p = 0.58$. Soluble in water, ether, CCl_4, and chloroform	Inhalation	Negative in rats and mice	Not applicable
Tetralin CAS No. 119-64-2	NTP TR 561, April 2011	Negative	Negative in micronucleus	Log $p = 1.67$. Soluble in ether and aniline	Inhalation	Negative in rats and mice	Not applicable
Propargyl alcohol CAS No. 107-19-7	NTP TR 552, September 2008	Negative	Negative in vivo micronucleus	Log $p = -0.38$. Miscible in water and many organic solvents	Inhalation	Negative in rats and mice	Not applicable
α-Methylstyrene CAS No. 98-83-9	NTP TR 543, November 2007	Negative	Negative chromosome aberrations, positive SCEs, positive micronucleus	Log $p = 3.48$. Miscible in water and many organic solvents	Inhalation	Negative in rats and mice	Not applicable
Methyl isobutyl ketone CAS No. 108-10-1	NTP TR 538, February 2007	Negative	Negative in mouse lymphoma assay	Log $p = 1.31$. Miscible in water and many organic solvents	Inhalation	Negative in rats and mice	Not applicable
Stoddard solvent IIC CAS No. 64742-88-7	NTP TR 519, September 2004	Negative	In vivo micronucleus negative	Stoddard Solvent is the most widely used solvent in the paint industry. It is a white spirit/mineral spirit. Component Log $p = 3.16$–7.06	Inhalation	Negative in rats and mice	Not applicable
Decalin CAS No. 91-17-8	NTP TR 513, January 2005	Negative	Equivocal in micronucleus	Log $p = 4.8$. Soluble in water, alcohol, ether, and chloroform	Inhalation	Negative in rats and mice	Not applicable
Isobutene CAS No. 115-11-7	NTP TR 487, December 1998	Negative	Negative in micronucleus	Log $p = 2.34$. Soluble in water, alcohol, ether, and chloroform	Inhalation	Negative in rats and mice	Not applicable
2-Butoxyethanol CAS No. 111-76-2	NTP TR 484, March 2000	Negative	Negative in SCEs, chromosome aberrations	Log $p = 0.83$. Soluble in mineral oil, most organic solvents, and ethanol	Inhalation	Negative in rats and mice	Not applicable
Furfuryl alcohol CAS No. 98-00-0	NTP TR 482, February 1999	Negative	Positive in SCEs, negative in chromosome aberrations, negative in micronucleus	Log $p = 0.28$. Soluble in water, most oils, alcohol, and organic solvents	Inhalation	Negative in rats and mice	Not applicable
Tetrahydrofuran CAS No. 109-99-9	NTP TR 475, June 1998	Negative	Negative in SCE, chromosome aberrations, micronucleus	Log $p = 0.46$. Soluble in water, ethanol, and ketones	Inhalation	Negative in rats and mice	Not applicable
Isobutyraldehyde CAS No. 78-84-2	NTP TR 472, February 1999	Negative	Positive for SCEs and chromosome aberrations	Log $p = 0.77$. Soluble in water, ethanol, and ketones	Inhalation	Negative in rats and mice	Not applicable
Tetrafluoroethylene CAS No. 116-14-3	NTP TR 450, April 1997	Negative	Negative	Log $p = 1.21$ (est.). Soluble in water	Inhalation	Negative in rats and mice	Not applicable

(continued)

Table 8. (continued)

Chemical	Date	Ames assay test	Clastogen	Physicochemical characteristics[a]	Route of exposure	Lung tumors	Nonneoplastic findings
Acetonitrile CAS No. 75-05-8	NTP TR 447, April 1996	Negative	Weakly positive SCE and chromosome aberrations. Positive micronucleus male mice	Log $p = -0.34$. Soluble in water, alcohol, chloroform, and ether	Inhalation	Negative in rats and mice	Not applicable
Hexachlorocyclopentadiene CAS No. 77-47-4	NTP TR 437, February 1994	Negative	Negative in SCE, chromosome aberrations, micronucleus	Log $p = 5.04$. Soluble in water, acetone, CCl_4, and methanol	Inhalation	Negative in rats and mice	Not applicable
l-Epinephrine hydrochloride CAS No. 55-31-2	NTP TR 380, March 1990	Negative	Negative in SCE and chromosome aberrations	Log $p = -2.59$. Soluble in water	Inhalation	Negative in rats and mice	Not applicable
2-Chloroacetophenone CAS No. 532-27-4	NTP TR 379, March 1990	Negative	Weakly positive in chromosomal aberrations	Log $p = 1.93$ (est.). Soluble in ethanol, ether, and benzene	Inhalation	Negative in rats and mice	Not applicable
CS2 (94% o-chlorobenzalmalononitrile) CAS No. 2698-41-1	NTP TR 377, March 1990	Equivocal or negative	Positive in SCE and chromosome aberrations	Log $p = 2.76$. Soluble in acetone, methylene chloride, and benzene	Inhalation	Negative in rats and mice	Not applicable
Toluene CAS No. 108-88-3	NTP TR 371, February 1990	Negative	Negative	Log $p = 2.73$. Soluble in ethanol, benzene, ether, and carbon sulfide	Inhalation	Negative in rats and mice	Not applicable
Methyl methacrylate CAS No. 80-62-6	NTP TR 314, October 1986	Negative	Positive for SCEs and chromosome aberrations	Log $p = 1.38$. Soluble in water and most organic solvents	Inhalation	Negative in rats and mice	Not applicable
Tetrachloroethylene (perchloroethylene) CAS No. 127-18-4	NTP TR 311, August 1986	Negative	Negative	Log $p = 3.40$. Soluble in water, ethanol, chloroform, and benzene	Inhalation	Negative in rats and mice	Not applicable
Propylene oxide CAS No. 75-56-9	NTP TR 267, March 1985	Negative	Induces DNA strand breaks in human diploid fibroblasts	Log $p = 0.03$. Soluble in water, ethanol, and ether	Inhalation	Negative in rats and mice	Not applicable

NTP: National Toxicology Program.

[a]All physicochemical values are from the Hazardous Substances Database unless otherwise designated.

Table 9. 1/58 Total NTP inhalation studies conducted in rats and mice are positive in the Ames assay test and show lung tumors in neither rats nor mice.

Chemical	Date	Ames assay test	Clastogen	Physicochemical characteristics[a]	Route of exposure	Lung tumors	Nonneoplastic findings
Propylene glycol mono-*t*-butyl ether CAS No. 57018-52-7	NTP TR 515, March 2004	Positive in TA97 without S9	Negative in SCE and chromosome aberrations; small positive micronucleus	Log $p = 0.87$ (est.). Soluble in water.	Inhalation	Negative in rats and mice	

NTP: National Toxicology Program.
[a]All physicochemical values are from the Hazardous Substances Database unless otherwise designated.

only cause tumors outside the lung was 25/58 (43.1%) in rats and 10/58 (17.2%) in mice (p-value$_1$ = 0.0024; p-value$_2$ = 0.0016). The fraction of agents that are both positive in the Ames assay test and only cause lung tumors is 1/58 (1.7%) in rats and 6/58 (10.3%) in mice (p-value$_1$= 0.0512; p-value$_2$ = 0.0477). The fraction of agents that are both positive in the Ames assay test and only cause tumors outside the lung is 14/58 (24.1%) in rats and 1/58 (1.7%) in mice (p-value$_1$ = 0.0003; p-value$_2$ <0.0001). The fraction of agents that cause tumors outside the lung in only one rodent species is 16/58 (27.6%) in rats and 0/58 in mice (p-value$_1$ = <0.0001; p-value$_2$ <0.0001).

Eleven out of 58 agents tested in the NTP inhalation studies using rats and mice were negative in the Ames assay test and showed lung tumors in mice only (Table 2). Ten of the 11 chemicals (90.9%) in Table 2 are insoluble or slightly soluble in water, soluble in organic solvents, and have moderately hydrophobic log base 10 octanol–water partition coefficients of 0.17, 1.85, 2.10, 2.13, 2.42, 2.53, 2.61, 3.15, 3.30, 3.66, and 3.80. These moderate log p (log K_{ow}) values are near the optimum values for penetrating the lipid bilayer membranes of cells.[15] These chemicals induce hyperplasia in the airways of mice. Hyperplasia is an increase in the number of cells resulting from cellular proliferation.[16]

Three out of 58 agents tested in the NTP inhalation studies using rats and mice were negative in the Ames assay test and showed lung tumors in rats only (Table 3). These three agents contain metals and are not soluble in water. When laboratory rats are exposed to inorganic particles to the point that lung overload occurs, both benign and malignant tumors may develop. Rats exhibit relatively fast pulmonary clearance of dust and appear to retain pulmonary burdens of dust predominantly in macrophages within alveoli. Mice do not experience similar particle overload effects.[17]

Five out of 58 (8.6%) agents tested in the NTP inhalation studies using rats and mice were negative in the Ames assay test and showed lung tumors in both rats and mice (Table 4). Four out of five agents (80%) in Table 4 are powdered metals. One of the five (20%), Trim VX is a water-soluble oil that forms a chemical emulsion. Each of these five agents caused inflammation and hyperplasia in the lungs. In Table 5, 9/58 (15.5%) agents tested in NTP inhalation studies conducted in rats and mice were positive in the Ames assay test and showed lung tumors in both rats and mice. Three out of nine (33.3%) of these agents were metals.

In Table 6, 6/58 (10.3%) of the total NTP studies conducted using rats and mice were positive in the Ames assay test and showed lung tumors in mice only. All six of these chemicals were direct acting Ames assay mutagens that did not require metabolic activation by rat liver S9 to display mutagenicity. Table 7 shows a stark contrast with the results from Table 6. In Table 7, only 1/58 (1.7%) of the total NTP inhalation studies conducted in rats and mice reported an agent that was positive in the Ames assay test and displayed lung tumors in rats only. In addition, this one positive result might be spurious as the maximum exposure dose in mice was only ¼ the maximum dose in rats due to lethality of 1,2-epoxybutane in mice.

In Table 8, 22/58 (37.9%) total NTP inhalation studies conducted in rats and mice were negative in the Ames assay test and did not show lung tumors in either rats or mice. Since these 22 agents did not show neoplastic changes in the lungs, nonneoplastic changes are not shown for this group of compounds. A number of these agents are either relatively water soluble with log p's of −2.59, −0.38, −0.34, 0.055, 0.28, 0.46, 0.58, 0.77, and 0.83 or extremely hydrophobic with log p's of 4.8, 5.04, and a range of 3.16–7.06 for a multicomponent mixture. Whether these 12 log p values that fall outside the optimum cellular penetration range of about log p of 2[11] reduced their ability to penetrate the lung epithelial cells of the rodents thereby reducing their potential tumorigenicity is unknown.

Table 9 shows that propylene glycol mono-*t*-butyl ether is the only chemical tested via inhalation by NTP in rats and mice reported to be both Ames assay positive and lacking lung tumors in either rats or mice, that is, 1/58 (1.7%). This result is questionable as the only Ames assay data available was a single positive result in Ames assay *Salmonella* strain TA97 without metabolic activation by rat liver S9. Table 10 shows that Ames assay test data were lacking for 2/58 (3.4%) of the total NTP inhalation studies conducted in rats and mice, that is, nickel sulfate hexahydrate which did not cause lung tumors in either rats or mice, and indium phosphide which did cause lung tumors in male and female rats and in male and female mice.

Table 10. 2/58 Total NTP inhalation studies conducted in rats and mice for compounds lacking Ames assay test data.

Chemical	Date	Ames assay test	Clastogen	Physicochemical characteristics	Route of exposure	Lung tumors	Nonneoplastic findings
Nickel sulfate hexahydrate CAS No. 10101-97-0	NTP TR 454, July 1996	No data	Nickel sulfate hexahydrate (500 to 800 g/mL) was tested for induction of trifluorothymidine resistance in L5178Y mouse lymphoma cells. A positive response was observed in the absence of S9. The test was not performed with S9	Soluble in water and ammonium hydroxide	Inhalation	Negative in rats and mice	The incidences of chronic active inflammation, macrophage hyperplasia, alveolar proteinosis, and fibrosis were markedly increased in male and female rats exposed to 0.25 or 0.5 mg/m^3. Inflammatory lesions of the lung generally occurred in all exposed groups of male and female mice at the end of the 2-year study. These lesions included macrophage hyperplasia, chronic active inflammation, bronchialization (alveolar epithelial hyperplasia), alveolar proteinosis, and infiltrating cells in the interstitium
Indium phosphide CAS No. 22398-80-7	NTP TR 499, July 2001	No data	Negative in micronucleus	Slightly soluble in acid	Inhalation	Clear evidence in male rats, female rats, male mice, female mice	Chronic active inflammation in mouse lung; atypical hyperplasia and inflammation in rat lung

NTP: National Toxicology Program.

Table 11 shows 7/58 (12.1%) cases where a compound caused tumors in the rat lung, but not outside the lung. Of the seven compounds, four are metals. The seven compounds are as follows: tetranitromethane, isobutyl nitrite, antimony trioxide, vanadium pentoxide, chromium hexavalent compounds, Trim VX, and molybdenum trioxide. Table 11 shows 15/58 (25.9%) cases where a compound only caused tumors in the mouse lung, but not outside the lung. Of the 15 compounds, seven are metals (46.7%). The 15 compounds are as follows: cobalt metal, tetranitromethane, cobalt sulfate heptahydrate, isobutyl nitrite, antimony trioxide, vanadium pentoxide, chromium hexavalent compounds, bis(chloromethyl)ether, Trim VX, nickel oxide, molybdenum trioxide, ozone, vinylidene chloride, naphthalene, and divinylbenzene-HP. All of the seven compounds that caused tumors in the rat lung, but did not cause tumors at other anatomical sites in the rat, also caused tumors in the mouse lung.

Further examination of Table 11 shows that in 34/58 (58.6%) of the compounds tested via inhalation, rats did not show a lung tumor but did show a tumor at another anatomical site outside the lung. In every one of these 34 cases, the chemical was not a metal. The 34 chemicals are as follows: 1,3-butadiene, trichloroethylene, cumene, dichloromethane, isoprene, nitromethane, chloroprene, 1,2-dibromo-3-chloropropane, nitrobenzene, chloroethane, naphthalene, ethylbenzene, CIMSTAR, divinylbenzene-HP, allyl glycidyl ether, propylene glycol mono-*t*-butyl ether, tetralin, propargyl alcohol, α-methylstyrene, methyl isobutyl ketone, Stoddard Solvent IIC, decalin, isobutene, 2-butoxyethanol, furfuryl alcohol, tetrahydrofuran, tetrafluoroethylene, acetonitrile, hexachlorocyclopentadiene, 2-chloroacetophenone, tetrachloroethylene, and propylene oxide.

In contrast with the results for rats, only 10/58 (17.2%) of the compounds tested via inhalation displayed a pattern of no lung tumors in mice, but presentation of tumors at other sites outside the lung. The 10 chemicals are as follows: propylene glycol mono-*t*-butyl ether, propargyl alcohol, methyl isobutyl ketone, Stoddard Solvent IIC, decalin, furfuryl alcohol, tetrahydrofuran, tetrafluoroethylene, tetrachloroethylene, and propylene oxide. All of the 10 compounds that caused tumors at anatomical sites outside the lung, but did not cause lung tumors in mice, also displayed the same tumor presentation pattern in rats.

In Table 11, each of the 58 compounds for which data were available were ranked in descending order of their potential to induce lung tumors in the lungs of rats and mice. Two out of three substances ranked at the highest level of rodent pulmonary tumorigenicity were metals. The compound ranked at the second highest level of pulmonary tumorigenicity to rodent lung was a metal. One of the two compounds ranked at the third highest level of pulmonary tumorigenicity to rodent lung was a metal. In addition, the compound ranked at the fourth highest level of pulmonary tumorigenicity to rodent lung was also a metal. Therefore, 5/7 of the most potent compounds for inducing tumors in the lungs of rats and mice were metals.

Table 11. Relative ranking by lung tumor-producing potency of 58 substances tested via inhalation by NTP in rats and mice (cadmium and cadmium compounds; and diesel exhaust particulates omitted for lack of results regarding a particular compound).

Agent	Lung tumor rank	Ames assay +/−	Clastogen +/−	Log Kow	Lung tumor presentation	Tumors at other organ sites
Indium phosphide CAS No. 22398-80-7	1	No data	Negative	Not applicable because metallic, not soluble in water	Clear evidence in male rats, female rats, male mice, female mice	Yes—rats; Yes—mice
Cobalt metal CAS No. 7440-48-4	1	Positive	Negative	Not applicable because a metal; only ultrafine cobalt metal is soluble in water	Clear evidence in male rats, female rats, male mice, female mice	Yes—rats; No—mice
Tetranitromethane CAS No. 509-14-8	1	Positive	Positive	Log $p = -2.05$	Clear evidence in male rats, female rats, male mice, female mice	No—rats; No—mice
Cobalt sulfate CAS No. 10124-43-3 cobalt sulfate heptahydrate	2	Negative	Negative	Not applicable, soluble in water	Some evidence in male rats; clear evidence in female rats, male mice, female mice	Yes—rats; No—mice
Isobutyl nitrite CAS No. 542-56-3	3	Positive	Positive in SCE and chromosome aberrations	Log $p = 2.31$	There was clear evidence of carcinogenic activity of isobutyl nitrite in male and female F344/N rats based on the increased incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined). There was some evidence of carcinogenic activity of isobutyl nitrite in male and female B6C3F$_1$ mice based on the increased incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) in males and females	No—rats; No—mice
Antimony trioxide CAS No. 1309-64-4	3	Positive comet assay in mouse lung tissue samples	Positive micronucleus	Not applicable because a metal; not soluble in water	*Some evidence of carcinogenic activity* of antimony trioxide in male and female Wistar Han rats based on increased combined incidences of alveolar/bronchiolar adenoma or carcinoma in the lung. Clear evidence in male and female mice	No—rats; No—mice
Vanadium pentoxide CAS No. 1314-62-1	4	Negative	Negative in micronucleus	Not applicable because a metal; dissolves slightly in water	Under the conditions of this 2-year inhalation study, there was some evidence of carcinogenic activity[a] of vanadium pentoxide in male F344/N rats and equivocal evidence of carcinogenic activity of vanadium pentoxide in female F344/N rats based on the occurrence of alveolar/bronchiolar neoplasms. There was clear evidence of carcinogenic activity of vanadium pentoxide in male and female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms	No—rats; No—mice

(continued)

Table 11. (continued)

Agent	Lung tumor rank	Ames assay +/−	Clastogen +/−	Log Kow	Lung tumor presentation	Tumors at other organ sites
1,2-Dibromoethane CAS No. 106-93-4	5	Positive—direct acting mutagen	Positive in SCE and DNA binding	Log $p = 1.96$. Soluble in water and most organic solvents	Positive in male and female mice and in female rats. Negative in male rats	Yes—rats; Yes—mice
Chromium hexavalent compounds CAS No. 18540-29-9	6 (no info re rodent sex)	Positive	Positive	Not applicable because a metal	Exposure to chromium(VI) compounds (calcium chromate, chromium trioxide, or sodium dichromate) via inhalation or intratracheal or intrabronchial implantation caused benign and/or malignant lung tumors in rats and/or mice	No—rats; No—mice
Bis(chloromethyl) ether and technical grade chloromethyl methyl ether CAS Nos. 542-88-1 and 107-30-2	6 (no info re rodent sex)	Positive alkylating agent	Positive	Log $p = -0.38$. Reacts with water	Exposure to BCME by inhalation caused lung tumors in rats (benign) and mice (carcinoma)	Ranking would probably be higher if had sex info. Yes—rats; No—mice
Trim VX	7	Negative	Negative	Not applicable—complex mixture	There was *equivocal evidence of carcinogenic activity* of Trim VX in male Wistar Han rats based on the combined occurrences of alveolar/bronchiolar adenoma or carcinoma of the lung. There was *equivocal evidence of carcinogenic activity* of Trim VX in female Wistar Han rats based on the occurrences of alveolar/bronchiolar adenoma of the lung. There was *clear evidence of carcinogenic activity* of Trim VX in male B6C3F1/N mice based on the increased combined incidences of alveolar/bronchiolar adenoma or carcinoma of the lung. There was clear evidence of carcinogenic activity of Trim VX in female B6C3F1/N mice based on the increased combined incidences of alveolar/bronchiolar adenoma or carcinoma (primarily carcinoma) of the lung	No—rats; No—mice
Nickel oxide CAS No. 1313-99-1	8	Negative	Negative in micronucleus; negative in chromosome aberrations	Not applicable because a metal; insoluble in water	Some evidence in male and female rats; equivocal evidence mice; negative in male mice	Yes—rats; No—mice
Molybdenum trioxide CAS No. 1313-27-5	8	Negative	Negative	Not applicable because a metal; in soluble in water	Equivocal evidence in male rats, some evidence of carcinogenic activity in male mice, some evidence in female mice	No—rats; No—mice
Bromoethane (ethyl bromide) CAS No. 74-96-4	9	Positive	Positive for SCEs and negative for chromo some aberrations	Log $p = 1.3$	Some evidence in male rats, equivocal evidence in female rats, equivocal evidence in male mice. Negative in female mice	Yes—rats; Yes—mice

(continued)

Table 11. (continued)

Agent	Lung tumor rank	Ames assay +/−	Clastogen +/−	Log Kow	Lung tumor presentation	Tumors at other organ sites
Nickel subsulfide CAS No. 12035-72-2	10	Negative	Positive	Not applicable because a metal; insoluble in water	Clear evidence in male and female rats; No evidence in male or female mice	Yes—rats; No—mice
1,3-Butadiene CAS No. 106-99-0	10	Positive	Positive	Log $p = 1.99$	Clear evidence in male and female mice; negative in rats	Yes—rats; Yes—mice
Trichloroethylene CAS No. 79-01-6	10	Negative	Probably negative (caused SCE only)	Log $p = 2.61$	Clear evidence in male and female mice; negative in rats	Yes—rats; Yes—mice
Cumene CAS No. 98-82-8	10	Negative	Positive (weak)	Log $p = 3.66$	Clear evidence in male and female mice; negative in rats	Yes—rats; Yes—mice
Dichloromethane (methylene chloride) CAS No. 75-09-2	10	Positive—direct acting Ames assay mutagen TA98 and TA100	Positive in chromosome aberrations	Log $p = 1.25$	Clear evidence of carcinogenicity in male and female mice; negative in rats	Yes—rats; Yes—mice
Isoprene CAS No. 78-79-5	10	Negative	Negative	Log $p = 2.42$	Positive in male and female mice; negative in rats	Yes—rats; Yes—mice
Nitromethane CAS No. 75-52-5	10	Negative	Negative	Log $p = 0.17$	Positive in male and female mice; negative in rats	Yes—rats; Yes—mice
Chloroprene CAS No. 126-99-8	10	Negative	Negative	Log $p = 2.53$	Positive in male and female mice; negative in rats	Yes—rats; Yes—mice
1,2-dibromo-3-chloropropane CAS No. 96-12-8	10	Positive to TA1535 without S9		Log $p = 2.96$	Positive in male and female mice; negative in rats	Yes—rats; Yes—mice
Ozone	11	Positive—direct mutagen in TA102		Log $p = -0.87$	There was *equivocal evidence* of carcinogenic activity of ozone in male B6C3F$_1$ mice based on increased incidences of alveolar/bronchiolar adenoma or carcinoma. There was *some evidence* of carcinogenic activity of ozone in female B6C3F$_1$ mice based on increased incidences of alveolar/bronchiolar adenoma or carcinoma. Negative in rats	No—rats; No—mice
Talc containing no asbestos fibers CAS No. 14807-96-6	12	Negative	Negative	Not applicable Insoluble in water	Clear evidence in female rats; no evidence in male rats, or male or female mice	Yes—rats; No—mice
Gallium arsenide CAS No. 1303-00-0	12	Negative	Negative in micronucleus assay	Not applicable because a metal; insoluble in water	No evidence male rats, clear evidence in female rats, no evidence in male and female mice	Yes—rats; No—mice
Nitrobenzene CAS No. 98-95-3	12	Negative	Positive	Log $p = 1.85$	Positive in male mice. Negative in female mice and rats	Yes—rats; Yes—mice

(continued)

Table 11. (continued)

Agent	Lung tumor rank	Ames assay +/−	Clastogen +/−	Log Kow	Lung tumor presentation	Tumors at other organ sites
Chloroethane (ethyl chloride) CAS No. 75-00-3	12	Positive to TA1535 without S9 alkylating agent		Log $p = 1.43$	Positive in male mice. Negative in female mice and rats	Yes—rats; Yes—mice
Vinylidene chloride CAS No. 75-35-4	12	Negative	Negative	Log $p = 2.13$	Incidence of alveolar/bronchiolar carcinoma significantly increased in 12.5 ppm female mice; negative in male mice and in rats	No—rats; No—mice
Naphthalene CAS No. 91-20-3	12	Negative	Positive	Log $p = 3.3$	Significantly increased incidence of benign lung tumors (adenoma) in female B6C3F1 mice	Yes—rats; No—mice
Ethylbenzene CAS No. 100-41-4	13	Negative	Negative for SCE or chromosome aberrations	Log $p = 3.15$	Some evidence of carcinogenic activity in male mice; negative in female mice and rats	Yes—rats; Yes—mice
CIMSTAR 3800	13	Direct mutagen *E. coli* but negative in TA98 and TA100; considered weakly positive	Negative in micronucleus in vivo	Not applicable—— multicomponent mixture	Some evidence of carcinogenic activity in female mice. Negative in male mice and rats	Yes—rats; Yes—mice
Divinylbenzene-HP CAS No. 1321-74-0	14	Negative	Negative	Log $p = 3.8$	Equivocal evidence of carcinogenic activity in female mice; negative in male mice, male and female rats	Yes—rats; No—mice
Allyl glycidyl ether CAS No. 106-92-3	15	Positive	Positive in SCE and chromosome aberrations	Solubility in water is 14%	No evidence of carcinogenic activity in male Osborne-Mendel rats, no evidence in female rats, no evidence in male mice, no evidence in female mice	Yes—rats; No—mice; nasal passages only
Propylene glycol mono-*t*-butyl ether CAS No. 57018-52-7	15	Positive in TA97 without S9	Negative in SCE and chromosome aberrations; small positive micronucleus	Log $p = 0.83$	Negative in rats and mice	Yes—rats; Yes—mice
Diethylamine CAS No. 109-89-7	15	Negative	Negative in micronucleus	Log $p = 0.58$	Negative in rats and mice	No—rats; No—mice
Tetralin CAS No. 119-64-2	15	Negative	Negative in micronucleus	Log $p = 1.67$	Negative in rats and mice	Yes—rats; No—mice
Propargyl alcohol CAS No. 107-19-7	15	Negative	Negative in vivo micronucleus	Log $p = -0.38$	Negative in rats and mice	Yes—rats; Yes—mice
α-Methylstyrene CAS No. 98-83-9	15	Negative	Negative chromosome aberrations, positive SCEs, positive micronucleus	Log $p = 3.48$	Negative in rats and mice	Yes—rats; Yes—mice
Methyl isobutyl ketone CAS No. 108-10-1	15	Negative		Log $p = 1.31$	Negative in rats and mice	Yes—rats; Yes—mice

(continued)

Table 11. (continued)

Agent	Lung tumor rank	Ames assay +/−	Clastogen +/−	Log Kow	Lung tumor presentation	Tumors at other organ sites
Stoddard solvent IIC CAS No. 64742-88-7	15	Negative	In vivo micronucleus negative	Not applicable—mixture	Negative in rats and mice	Yes—rats; Yes—mice
Decalin CAS No. 91-17-8	15	Negative	Equivocal in micronucleus	Log $p = 4.8$	Negative in rats and mice	Yes—rats; Yes—mice
Isobutene CAS No. 115-11-7	15	Negative	Negative in micronucleus	Log $p = 2.34$	Negative in rats and mice	Yes—rats; No—mice
2-Butoxyethanol CAS No. 111-76-2	15	Negative	Negative SCEs, chromosome aberrations	Log $p = 0.83$	Negative in rats and mice	Yes—rats; No—mice
Furfuryl alcohol CAS No. 98-00-0	15	Negative	Positive SCEs, negative chromosome aberrations, negative micronucleus	Log $p = 0.28$	Negative in rats and mice	Yes—rats; Yes—mice
Tetrahydrofuran CAS No. 109-99-9	15	Negative	Negative in SCE, chromosome aberrations, micronucleus	Log $p = 0.46$	Negative in rats and mice	Yes—rats; Yes—mice
Isobutyraldehyde CAS No. 78-84-2	15	Negative	Positive for SCEs and chromosome aberrations	Log $p = 0.77$	Negative in rats and mice	No—rats; No—mice
Tetrafluoroethylene CAS No. 116-14-3	15	Negative	Negative	Log $p = 1.21$	Negative in rats and mice	Yes—rats; Yes—mice
Acetonitrile CAS No. 75-05-8	15	Negative	Weakly positive SCE and chromosome aberrations. Positive micronucleus male mice	Log $p = -0.34$	Negative in rats and mice	Yes—rats; No—mice
Hexachlorocyclopentadiene CAS No. 77-47-4	15	Negative	Negative in SCE, chromosome aberrations, micronucleus	Log $p = 5.04$	Negative in rats and mice	Yes—rats; No—mice
l-Epinephrine hydrochloride CAS No. 55-31-2	15	Negative	Negative in SCE and chromosome aberrations	Log $p = -2.59$	Negative in rats and mice	No—rats; No—mice; doses considered too low
2-Chloroacetophenone CAS No. 532-27-4	15	Negative	Weakly positive in chromosome aberrations	Log $p = 1.93$	Negative in rats and mice	Yes—rats; No—mice

(continued)

Table 11. (continued)

Agent	Lung tumor rank	Ames assay +/−	Clastogen +/−	Log Kow	Lung tumor presentation	Tumors at other organ sites
CS2 (94% o-chlorobenzalmalononitrile) CAS No. 2698-41-1	15	Equivocal or neg	Positive in SCE and chromosome aberrations	Log $p = 2.76$	Negative in rats and mice	No—rats; No—mice
Toluene CAS No. 108-88-3	15	Negative	Negative	Log $p = 2.73$	Negative in rats and mice	No—rats; No—mice
Methyl methacrylate CAS No. 80-62-6	15	Negative	Positive for SCEs and chromosome aberrations	Log $p = 1.38$	Negative in rats and mice	No—rats; No—mice
Tetrachloroethylene (perchloroethylene) CAS No. 127-18-4	15	Negative	Negative	Log $p = 3.40$	Negative in rats and mice	Yes—rats; Yes—mice
Propylene oxide CAS No. 75-56-9	15	Negative		Log $p = 0.055$	Negative in rats and mice	Yes—rats (nasal turbinates); Yes—mice (nasal turbinates)
Nickel sulfate hexahydrate CAS No. 10101-97-0	15	No data	Nickel sulfate hexahydrate (500 to 800 g/mL) was tested for induction of trifluorothymidine resistance in L5178Y mouse lymphoma cells. A positive response was observed in the absence of S9. The test was not performed with S9	Not applicable because a metal	Negative in rats and mice	No—rats; No—mice

NTP: National Toxicology Program.
Clear Evidence > Some Evidence > Equivocal Evidence > No Evidence
[a]All physicochemical values are from the Hazardous Substances Database unless otherwise designated.

Table 11 also compares the concordance between rats and mice for each of the 58 compounds tested via the inhalation route to induce tumors at organ sites outside the lung. For 26/58 (44.8%) compounds, both rats and mice showed development of another tumor type outside of the lung. That is, there were 26 cases of positive concordance for development of tumors outside the lung when tested by the inhalation route. Herein follows the unusual result from Table 11. For 16/58 (27.6%) compounds, rats showed tumors outside the lungs while similarly tested mice did not show tumors outside the lungs. In contrast, there is a not a single case where mice showed a tumor outside the lungs while a similarly tested rat did not show a tumor outside the lungs—0/58 compounds.

The entire list of the 10 compounds negative in mouse lung, but positive at other sites, is contained within the list of 34 compounds negative in rat lung but positive at other sites.

In Table 11, there were seven compounds (7/58, 12.1%) which produced neither lung tumors nor tumors at other anatomical sites in either rats or mice. These seven completely negative compounds are as follows: diethylamine, isobutyraldehyde, *l*-epinephrine hydrochloride, CS2 (94% *o*-chlorobenzalmalononitrile), toluene, methyl methacrylate, and nickel sulfate hexahydrate. Ames assay test data were available for 6/7 (85.7%) with the exception of nickel sulfate hexahydrate. All of the six Ames assay tests conducted on these compounds were negative.

In Table 11, indium phosphide was the only compound that produced lung tumors in male and female rats, male and female mice, and at other anatomical sites in both rats and mice. Indium phosphide ranked as the most clearly tumorigenic compound to rodent lung of the 58 tested to date via inhalation by NTP.

Conclusion

For the 58 compounds tested via inhalation by NTP, there is a high degree of discordance between rats and mice in the susceptibility to develop lung tumors. The causation of tumors at anatomical sites outside the lung via the inhalation route is also discordant in rats and mice. This high degree of discordance in the results of two-year inhalation assays suggests that different mechanisms of carcinogenesis might play lesser or greater roles in the development of pulmonary tumors in the two species. In cases where the results from two-year inhalation studies are concordant for lung tumors, the concordant agent might be of special concern to human risk assessment.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Comments of Safer Chemicals Healthy Families on Risk Evaluation Scoping Documents for Ten Chemical Substances under the Toxic Substances Control Act

Submitted via Regulations.gov (September 19, 2017)

1,4-Dioxane. Docket ID No.: EPA-HQ-OPPT-2016-0723.

1-Bromopropane. Docket ID No.: EPA-HQ-OPPT-2016-0741.

Asbestos. Docket ID No.: EPA-HQ-OPPT-2016-0736.

Carbon Tetrachloride. Docket ID No.: EPA-HQ-OPPT-2016-0733.

Cyclic Aliphatic Bromide Cluster (Hexabromocyclododecane or HBCD). Docket ID No.: EPA-HQ-OPPT-2016-0735.

Methylene Chloride. Docket ID No.: EPA-HQ-OPPT-2016-0742.

N-Methylpyrrolidone (NMP). Docket ID No.: EPA-HQ-OPPT-2016-0743.

Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f]diisoquinoline-1,3,8,10(2H,9H)-tetrone). Docket ID No.: EPA-HQ-OPPT-2016-0725.

Trichloroethylene (TCE). Docket ID No.: EPA-HQ-OPPT-2016-0737.

Tetrachloroethylene (also known as Perchloroethylene). Docket ID No.: EPA-HQ-OPPT-2016-0732.

INTRODUCTION AND SUMMARY

Safer Chemicals, Health Families (SCHF), Earthjustice, Natural Resources Defense Council (NRDC), Environmental Health Strategy Center, Toxic-Free Future and Asbestos Disease Awareness Organization (ADAO) submit these comments on the scoping documents developed by the Environmental Protection Agency (EPA) on the initial 10 chemicals selected for risk evaluations under the newly enacted Frank R. Lautenberg Chemical Safety for the 21st Century Act (LCSA). These organizations are committed to enhancing the safety of chemicals used in homes, workplaces and products and strongly support effective and health-protective implementation of the LCSA.

Through LCSA, Congress amended the Toxic Substances Control Act (TSCA) to establish a new framework for conducting timely, comprehensive and science-based risk evaluations for chemicals of concern. The law provides that EPA's evaluations must be strictly risk-based and must result in a definitive determination of whether the evaluated substance as a whole presents an unreasonable risk of injury to health and the environment across its life cycle, without regard to cost and other non-risk factors.

Congress wanted EPA to launch the risk evaluation process expeditiously. Accordingly, in section 6(b)(2)(A) of TSCA, it directed EPA to assure that evaluations are initiated within six months of the law's enactment on 10 substances drawn from the 2014 TSCA Workplan list. EPA designated these 10 substances on December 19, 2016,[1] and following a public meeting and comment period, released draft scoping documents on June 22. Soon thereafter, EPA announced that it was developing problem formulation documents on the 10 chemicals and would release them for further comment by the end of the year. It also requested comments on the scoping documents in order to inform its approach to problem formulation.[2]

These comments address general issues common to the 10 chemicals as well as several chemical-specific issues. We are submitting our comments to all ten of the EPA dockets. The comments build on earlier submissions by these groups, including our March 15 comments on the scoping process and our July 24 letter to the Agency providing initial reactions to the 10 scoping documents. We have coordinated with a number of other public health and scientific organizations in developing comments on the scoping documents and generally support their recommendations.

The main messages and key recommendations in our comments are as follows:

- Problem formulation can fill gaps in scoping documents and enhance their depth of analysis but cannot be used to remove uses, exposures and hazards from the risk evaluation scope
- EPA should use problem formulation to provide more detail on the potentially exposed and susceptible subpopulations it will consider and how risks to these subpopulations will be determined
- Problem formulations should also describe EPA's strategies for assessing risks from aggregate and cumulative exposures
- Ongoing use and disposal of chemical products that are no longer being manufactured fall within the TSCA definition of "conditions of use" and must be included in problem formulations and assessed in risk evaluations
- Chemicals with ozone depletion and global warming potential pose environmental and health risks that fall within the scope of TSCA risk evaluations
- EPA risk evaluations should not reassess uses of trichloroethylene (TCE), methylene chloride (MC) and N-Methylpyrrolidone (NMP) that were fully assessed in its proposed section 6(a) rules, although these exposure pathways should be included in its determinations of aggregate exposure to these chemicals
- In the course of TSCA risk evaluations, EPA should not revisit definitive findings in IRIS assessments since these assessments represent the Agency's authoritative, peer reviewed determinations on the health effects of the chemicals they address
- In evaluating workplace risks, EPA should recognize and account for the uneven use and effectiveness of engineering controls, labeling and personal protective equipment in preventing occupational exposure and determine risks to workers in situations where these measures are not in place or ineffective
- EPA should not exclude from the 1,4-dioxane evaluation its production as a byproduct or impurity, which is a significant source of contamination of water sources and cancer risk

[1] 81 Federal Register 91927
[2] 82 Fed. Reg. 31,592 (July 7, 2017).

- In order to apply these general principles and fill other gaps in its scoping documents, these documents must be expanded and strengthened in several specific respects during problem formulation
- EPA should not prejudge the absence of adverse effects for particular end-points at the scoping stage but should defer such conclusions until the systematic review phase of its risk evaluation as the law requires
- Problem formulations should highlight aspects of use and exposure where available information is insufficient and request or require submission of this information by industry and other interested parties
- EPA needs to take stronger steps to limit CBI treatment of critical information during the risk evaluation process so that transparency and public participation in that process are not impaired

I. PROBLEM FORMULATION CAN FILL GAPS IN SCOPING DOCUMENTS AND ENHANCE THEIR DEPTH OF ANALYSIS BUT CANNOT BE USED TO REMOVE USES, EXPOSURES AND HAZARDS FROM THE RISK EVALUATION SCOPE

The 10 chemicals undergoing risk evaluations have widespread and substantial exposure and multiple adverse health effects. Comprehensive and health protective assessments of their safety are essential to safeguard communities and vulnerable populations and to set a precedent for strong and effective implementation of the new law. For this reason, our groups made a significant investment in characterizing the use and exposure profiles of several of the 10 chemicals and provided extensive submissions to the Agency to help inform its scoping documents for these chemicals.

The scoping documents represent a considerable amount of work in a short period of time and provide a helpful starting point for the 10 evaluations. However, the July 7 Federal Register notice announcing the availability of the scoping documents acknowledges that the Agency was unable to process all the information gathered during the scoping process and that the scoping documents were not as "refined or specific" as EPA had hoped. We agree with this assessment and believe that the scoping documents contain serious gaps, lack sufficient information on use and exposure, impose questionable limitations on the risk scenarios to be examined and fail to provide a roadmap to key elements of assessment methodology. These shortcomings reduce the utility of the scoping documents in laying the groundwork for well-informed and rigorous risk evaluations.

Given their limitations, we believe that expanding and strengthening the scoping documents through a problem formulation process is appropriate in this instance. However, neither LCSA nor the recently promulgated risk evaluation process rule refers to or authorizes problem formulation. Because it has no basis in the law, we oppose using problem formulation to narrow the scope of risk evaluations by deleting conditions of use, exposure pathways or health or environmental end-points identified in the June scoping documents. Section 6(b)(4)(D) of amended TSCA provides that, "not later than 6 months after the initiation of a risk evaluation," EPA must "publish the scope of the risk evaluation to be conducted, including the hazards, exposures, conditions of use and the potentially exposed or susceptible subpopulations the Administrator expects to consider." EPA met this requirement in its June scoping documents. The law provides no basis for EPA to remove uses, hazards or exposures from a risk

evaluation after its scope has been established in accordance with section 6(b)(4)(D).[3] Since problem formulation is not a recognized step in the risk evaluation process or a substitute for scoping under LCSA, it cannot be used narrow a risk evaluation's scope after-the-fact.

We do support, however, using problem formulation to provide more detail on the conditions of use, potentially exposed and susceptible subpopulations, and exposure pathways that EPA will evaluate as well as further explanation of the methodologies that EPA will use in its analysis of these and other risk assessment elements. This will help better structure the risk evaluations, assure that all relevant information is considered, and characterize more fully the conditions of use to be evaluated – without narrowing the risk evaluation scope.

II. EPA SHOULD USE PROBLEM FORMULATION TO PROVIDE MORE DETAIL ON THE POTENTIALLY EXPOSED AND SUSCEPTIBLE SUBPOPULATIONS IT WILL CONSIDER AND HOW RISKS TO THESE SUBPOPULATIONS WILL BE DETERMINED

One area that would benefit from greater elaboration during problem formulation is the identification of potentially exposed or susceptible subpopulations that require consideration in risk evaluations under TSCA section 6(b)(4)(F). The scoping documents provide nearly identical general "boilerplate" descriptions of such subpopulations. Further particulars on the size, geographic location, demographic characteristics and exposure profile of each subpopulation EPA has identified would provide helpful assurance that the risks to that subpopulation will be characterized with the rigor that TSCA requires.

It is also critical for EPA to spell out the methodology it intends to use to determine the nature and magnitude of the risks that chemicals pose to each subpopulation. Such subpopulations are often comprised of low income and/or people of color and exposed to a disproportionate share of pollution, environmental hazards, and social and economic stressors. Multiple exposures to chemical and non-chemical stressors collectively increase the risk of harm, combined with synergistic effects with other health stressors such as limited access to quality health care.[4,5] EPA's risk evaluations need to fully account for these factors and its problem formulations should explain how it intends to do so.

In regard to greater susceptibility, the following are well-known factors that increase biologic sensitivity or reduce resilience to exposures,[6,7] and should be considered consistently for all 10 chemicals to identify susceptible subpopulations:

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[3] EPA's final risk evaluation rule, in contrast to its proposal, would permit the Agency to select which conditions of use to include in risk evaluation scopes as opposed to including all such uses. 82 Fed. Reg. 33,726 (July 20, 2017). Our groups argued in their comments on the proposal that the law required the Agency to address all conditions of use in its risk evaluations, as was recognized in the Agency's original proposal. Along with several other groups, we are challenging EPA's contrary interpretation in its petition for judicial review of the risk evaluation rule. Regardless of the outcome of this challenge, we believe that EPA has no basis to narrow the risk evaluation to exclude conditions of use once they have been included in its scope.

[4] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff. 2011;30(5):879–87.

[5] Vesterinen HM, Morello-Frosch R, Sen S, Zeise L, Woodruff TJ. Cumulative effects of prenatal-exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the human and animal evidence. Meliker J, editor. PLoS One. 2017 Jul 12;12(7):e0176331.

[6] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff. 2011;30(5):879–87.

Intrinsic/ endogenous factors

- Genetic polymorphisms/ genetics/ genetic makeup
- Health status/ nutritional status/ disease status/ pre-existing conditions
- Prenatal life stage
- Age

Extrinsic factors

- Multiple exposures/ co-exposures
- Race/ ethnicity
- Socioeconomic status (SES)

For example, the prenatal life stage is the most sensitive to developmental and reproductive toxicants, and women of childbearing age should be considered as a susceptible subpopulation for any chemical with such hazards. However, women of reproductive age are not identified as a potential susceptible subpopulation in the scoping documents for pigment violet 29, TCE, NMP, PERC, or HBCD, even though EPA will consider reproductive and developmental toxicity hazards for these chemicals. This omission should be corrected during problem formulation.

III. PROBLEM FORMULATION MUST DESCRIBE EPA'S STRATEGIES FOR ASSESSING RISKS FROM AGGREGATE AND CUMULATIVE EXPOSURES

Problem formulation should also address more fully how EPA intends to address the risks resulting from cumulative and aggregate exposures to each of the 10 chemicals. The scoping documents provide minimal discussion of this essential aspect of risk evaluation design.

Section 6(b)(4)(F)(ii) requires risk evaluations to describe whether aggregate or sentinel exposures to a chemical were considered and the basis for that consideration. To properly apply either or both of these approaches in a risk evaluation, EPA must determine in advance what methodology it will employ and then incorporate it in the risk evaluation design in sufficient detail to describe the key data sources it will use to assess exposure and how they will be used. The scoping documents fail to do this. EPA should remedy this gap in problem formulation.

We believe aggregate exposure assessment will be required for all of the 10 chemicals.[8] The focus of the new law is on determining risk based on all relevant pathways and sources of exposure for the general population and vulnerable subpopulations throughout a chemical's life cycle. Thus, under section 6(b)(4)(F)(i), EPA must "integrate and assess available information on hazards and exposures for *the conditions of use* of the chemical substance" and, under section 6(b)(4)(F)(iv), must "take into account, where relevant, the likely duration, intensity, frequency and number of exposures under *the conditions of use* of the chemical substance." This emphasis on integrating risk and exposure factors across a chemical's conditions of use necessarily requires the Agency to identify all sources of exposure that may affect the general population or specific subpopulations and to determine the overall levels, frequency

[7] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009.

[8] When analyzing aggregate exposures, "sentinel exposure" may be considered simultaneously, where appropriate. However, these are not mutually exclusive and EPA should not incorporate sentinel to the exclusion of aggregate.

and duration of exposures by each population or subpopulation resulting from this combination of pathways.[9]

EPA has applied the tools of "aggregate exposure assessment" successfully in several programs. For example, the 1996 Food Quality Protection Act (FQPA) directs EPA to examine aggregate exposures when issuing or renewing tolerances for pesticides in food and EPA has longstanding guidance for doing aggregate risk and exposure assessments to meet this requirement.[10]

During problem formulation, EPA should develop a roadmap for each of the 10 chemicals showing what steps it is taking to gather the necessary information for aggregate exposure assessment and how it will calculate or estimate the combined exposures resulting from multiple pathways or uses for the general population and potentially exposed or susceptible subpopulations.

Problem formulations should also address whether and how EPA will use "cumulative risk" methodologies for the first 10 risk evaluations. This, too, is an area that EPA has addressed in several guidance documents.[11] The Agency defines "cumulative risk" as "the combined risks from aggregate exposures (i.e., multiple route exposures) to multiple agents or stressors" and has explained that:

> "In cumulative risk assessments that examine risks posed by multiple chemicals, exposure assessments evaluate a population's chemical exposures through multiple routes of exposure over time. Such assessments may encompass multiple exposure timeframes in which the timing and intensity of exposures to different chemicals are examined relative to each other. It is also important to determine whether the exposures to multiple chemicals can lead to toxicokinetic interactions or toxicodynamic interactions. In addition to providing information about multiple chemical exposures in the general population, these exposure assessments identify potentially susceptible or vulnerable subpopulations in the study area and potentially unique pathways of exposure in those subpopulations."[12]

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[9] Exposures from TSCA-exempt uses such as personal care products or biocides should also be included in scoping documents and risk evaluations because of the need to account for their contribution to aggregate risk, even though regulatory authority over these products is not available under TSCA but derives from other laws administered by EPA or agencies such as FDA. This is now standard practice in implementing the Food Quality Protection Act (FQPA). The scoping documents contain limited and incomplete information on exposures to the listed chemicals from non-TSCA uses.

[10] https://www.epa.gov/sites/production/files/2015-07/documents/aggregate.pdf

[11] E.g., *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity.* U.S. Environmental Protection Agency, Office of Pesticide Programs, Washington, DC. (2002) Available at http://www.epa.gov/oppfead1/trac/science/cumulative_guidance.pdf; *Framework for Cumulative Risk Assessment,* U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/600/P-02/001F (2004). Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944.

[12] EPA National Center for Environmental Assessment, *Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document,* at xxviii (August 2007).

The importance of examining risks posed by multiple chemicals with overlapping pathways of exposure and common adverse health effects was also underscored by the National Academy of Sciences (NAS) in its Phthalates and Cumulative Risk report.[13]

We recommend that, in its problem formulations, EPA should commit to perform cumulative risk assessments whenever a population or subpopulation exposed to the subject chemical is also exposed to other chemicals that have similar health effects. In this situation, total risk to the relevant population or subpopulation will be a function not just of exposure to the subject chemical in isolation but of combined exposure to that chemical and other chemicals which have additive or synergistic health effects.

A compelling case for examining cumulative risks will exist where EPA is in parallel conducting risk evaluations on multiple chemicals within a class that have similar chemical structures, conditions of use and adverse health effects. An example of such a grouping is the four solvents (TCE, PERC, MC and NMP) among the initial 10 chemicals: not only is it likely that workers and consumers are exposed to all or some of these solvents simultaneously but their common hazards (i.e. neurotoxicity, reproductive toxicity) are likely to magnify the risks of such concurrent exposures. The problem formulations for these four chemicals should recognize the need to examine the cumulative risks they present and describe how EPA will evaluate cumulative risk scenarios.

IV. ONGOING USE AND DISPOSAL OF CHEMICAL PRODUCTS THAT ARE NO LONGER BEING MANUFACTURED FALL WITHIN THE TSCA DEFINITION OF "CONDITIONS OF USE" AND MUST BE ASSESSED IN RISK EVALUATIONS

Several of the 10 chemicals – asbestos, perchloroethylene (PERC), TCE, MC, carbon tetrachloride (CTC) and hexabromocyclododecane (HBCD) – contribute to ongoing exposure and risk as a result of historical manufacturing and processing activities that have been discontinued. In many cases, the current and foreseeable risks associated with these activities are significant. Nonetheless, the scoping documents provide limited information about these risk and exposure scenarios and take the position that they are outside the scope of risk evaluations except possibly as a source of information about aggregate exposure. Each scoping document contains this statement:

> "EPA interprets the mandates under section 6(a)-(b) to conduct risk evaluations and any corresponding risk management to focus on uses for which manufacture, processing, or distribution in commerce is intended, known to be occurring, or reasonably foreseen (i.e., is prospective or on-going), rather than reaching back to evaluate the risks associated with legacy uses, associated disposal, and legacy disposal, and interprets the definition of "conditions of use" in that context. For instance, the conditions of use for purposes of section 6 might reasonably include the use of a chemical substance in insulation where the manufacture, processing or distribution in commerce for that use is prospective or on-going, but would not include the use of the chemical substance in previously installed insulation, if the manufacture, processing or distribution for that use is not prospective or on-going. In other words, EPA interprets the risk evaluation process of section 6 to focus on the continuing flow of chemical

[13] National Research Council. Committee on the Health Risks of Phthalates, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies. 2008. Phthalates and cumulative risk assessment: the task ahead. Washington, D.C.: National Academies Press.

substances from manufacture, processing and distribution in commerce into the use and disposal stages of their lifecycle. That said, in a particular risk evaluation, EPA may consider background exposures from legacy use, associated disposal, and legacy disposal as part of an assessment of aggregate exposure or as a tool to evaluate the risk of exposures resulting from non-legacy uses."[14]

We believe that EPA is incorrectly interpreting the provisions of LCSA. The definition of "conditions of use" in section 3(4) covers the "circumstances . . . under which a chemical substance is . . . known or reasonably foreseen to be . . . used or disposed of." Where a chemical is performing an ongoing *in situ* function as a result of previous manufacturing and processing activity, that function comprises a current "use" of the chemical that is "known" to be occurring.

For example, although asbestos may no longer be sold as insulation, the asbestos insulation installed in millions of US buildings continues to perform insulating functions and thus is a current ongoing "use" of asbestos. Installed asbestos-containing building materials (ACBMs) represent one of the largest sources of asbestos accessible to the general public in the US, and the largest asbestos-exposed population consists of people who occupy buildings and homes with ACBMs. Maintenance and construction activities involving ACBMs are also frequent and widespread and account for the largest present-day increase in mesothelioma illness and death in the US.[15]

Similarly, the Healthy Building Network estimates there are 66-132 million pounds (30,000-60,000 metric tons) of HBCD in insulation in existing buildings.[16] These ongoing insulation uses are and will continue to be critical sources of ongoing exposures. HBCD is also present in cars and furniture as a flame retardant and its use in these long-lived consumer articles will contribute to ongoing exposures for years to come.[17]

Equally important, the disposal of building materials or consumer products containing asbestos or HBCD is an ongoing occurrence as buildings are torn down or remodeled and cars and furniture are replaced. Thus, the resulting releases into the environment and communities comprise a "circumstance . . . under which [these chemicals] are . . . known or reasonably foreseen to be . . . disposed of." As "conditions of use" within the TSCA definition, these activities and the risks they present are likewise required to be addressed in risk evaluations under section 6(b). For both chemicals, the immediate and long-term exposures associated with disposal of *in situ* building materials and products are likely to be widespread and significant well into the future.

To exclude from risk evaluations ongoing and future exposures from *in situ* uses of discontinued products would create a sizable gap in the life-cycle assessments of risk that Congress directed EPA to conduct under the new law. This would deprive the public, scientists and regulators of a comprehensive

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[14] EPA, *Scope of the Risk Evaluation for Asbestos*, June 2017, at 8.

[15] US CDC study, "Malignant Mesothelioma Mortality – United States 1999 to 2005."

[16] Safer Chemicals, Healthy Families et al. Comments to the U.S. Environmental Protection Agency (EPA) on the Scope of its Risk Evaluation for the TSCA Work Plan Chemicals: CYCLIC ALIPHATIC BROMIDE CLUSTER or HEXABROMOCYCLODODECANE (HBCD). March 15, 2017. https://healthybuilding.net/uploads/files/saferchemicals-hbcd.pdf

[17] For chemicals like TCE and PERC, the uses that contributed to widespread contamination of groundwater and drinking water may in fact be uses for which these chemicals are still being sold, requiring EPA to include them in its risk evaluations even under its narrow interpretation of the law.

picture of one of the largest sources of continuing and future risk. One consequence would be that EPA would lack the scientific basis to ban resumption of the sale and distribution of discontinued products containing asbestos, HBCD and similar chemicals despite the unreasonable risks that they present. In addition, decision-makers would be unable to reduce ongoing exposures and impose safeguards against unsafe disposal because they would lack a meaningful risk evaluation to inform these actions. Just as TSCA provides authority to evaluate the risks associated with ongoing exposures from discontinued activities, so it gives EPA the authority under section 6(a) to reduce these risks, yet the Agency would be stymied by the absence of a risk evaluation that provides a basis for such regulation.[18]

In short, EPA must characterize and assess ongoing exposures from the use and disposal of discontinued products and determine the risks they present as part of its risk evaluations on the initial 10 chemicals. The scoping documents provide virtually no discussion of these sources of exposure to the 10 chemicals. Nothing in the law allows EPA to exclude these risks from its evaluations. EPA must correct this omission during problem formulation.

V. OZONE DEPLETION AND GLOBAL WARMING POTENTIAL POSE ENVIRONMENTAL AND HEALTH RISKS THAT FALL WITHIN THE SCOPE OF TSCA RISK EVALUATIONS

In earlier submissions, SCHF and its members highlighted data showing the high ozone depleting potential of MC, CTC and 1-Bromopropane (1-BP).[19] The scoping documents do not address these properties of the three chemicals. Nor do they examine the global warming potential (GWP) of any of the 10 chemicals. These omissions conflict with the express purpose of risk evaluations under section 6(b)(4)(A): to "determine whether a chemical substance presents an unreasonable risk of injury to health *or the environment"* (emphasis added). They also fail to meet the Agency's obligation under section 6(b)(4)(F)(i) to "integrate and assess information . . . that is relevant to specific risks of injury to health *or the environment"* (emphasis added). Ozone depletion and global warming potential clearly pose risks to the environment and they are also recognized risk factors for human health.[20,21] Nothing in the law allows EPA to exclude these risks from its evaluations.

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[18] For some chemicals like lead and asbestos, other laws administered by EPA address handling and disposal of *in situ* materials. The Agency may be able to refer the findings of its risk evaluations to the programs implementing these laws under TSCA section 9(b) in lieu of further regulation under section 6. However, there are no existing laws that address ongoing exposure from use and disposal of discontinued products containing HBCD, perfluorinated chemicals and other substances and therefore the availability of the protections afforded under section 6 of TSCA may be critical to addressing their risks.

[19] See Comments of Safer Chemicals Healthy Families on Risk Evaluation Scoping Documents for Ten Chemical Substances under the Toxic Substances Control Act, March 15, 2017.

[20] The human health risks of ozone depletion are well recognized by the Agency and documented, at least in part, on EPA's webpage, "Health and Environmental Effects of Ozone Layer Depletion:" "Ozone layer depletion increases the amount of UVB that reaches the Earth's surface. Laboratory and epidemiological studies demonstrate that UVB causes non-melanoma skin cancer and plays a major role in malignant melanoma development. In addition, UVB has been linked to the development of cataracts, a clouding of the eye's lens." https://www.epa.gov/ozone-layer-protection/health-and-environmental-effects-ozone-layer-depletion (Accessed 9-18-17)

[21] The human health risks of global warming were well recognized and documented, at least in part, by the agency prior to the arrival of Administrator Pruitt, as outlined in the legacy pages at: https://19january2017snapshot.epa.gov/climate-impacts/climate-impacts-human-health_.html While that page is being updated, "...to reflect EPA's priorities under the leadership of President Trump and Administrator Pruitt," the Agency still notes, "Climate change is having direct and indirect impacts on the health of people. More extreme

The EPA Office of Air and Radiation (OAR) has considerable expertise in both ozone depletion and global warming and has assessed some (but not all) of the 10 chemicals from the perspective of these concerns. OAR can help OCSPP draw on this prior work for its TSCA risk evaluations and perform new assessments for those chemicals whose ozone depletion and global warming impacts have not previously been examined. By addressing these impacts in TSCA risk evaluations, EPA will fulfill the law's goal of providing a comprehensive picture of environmental and health risks across the chemical's life cycle. In particular cases, it may also highlight contributors to ozone depletion and global warming that have been overlooked and may warrant restriction. Whether these impacts can be adequately addressed under the Clean Air Act (CAA) or under TSCA need not be determined in the risk evaluation itself and can be deferred to the later evaluation of risk management options under section 6(a).

VI. EPA RISK EVALUATIONS SHOULD NOT REASSESS USES OF TCE, MC AND NMP THAT WERE FULLY ASSESSED IN ITS PROPOSED SECTION 6(a) RULES

EPA has proposed to ban certain uses of TCE, MC and NMP under section 6(a) of amended TSCA.[22] As the basis for these proposed rules, EPA conducted comprehensive exposure and risk assessments on the targeted uses of the three chemicals. These assessments were subject to public comment and peer review both during their development and again as part of the rulemaking process.

In its scoping documents for the three chemicals, EPA indicates that it intends to rely on the completed assessments and will not "reassess" the targeted uses.[23] We strongly agree with this approach. It would be counterproductive for the Agency reopen these assessments for yet another round of public input and to redo the extensive analysis they contain simply so industry commenters can have another bite at the apple on findings they dislike. Moreover, we believe that the next step in the rulemakings is for EPA to issue final rules as quickly as possible. These rules, once issued, should close the book on the targeted uses and enable EPA to focus its risk evaluations on uses that have not yet been assessed. In its more comprehensive risk evaluations, however, EPA should incorporate its earlier assessments so that the exposures they describe can be accounted for in determining aggregate exposure to the three chemicals.

VII. EPA SHOULD NOT REVISIT DEFINITIVE FINDINGS IN IRIS ASSESSMENTS, WHICH REPRESENT THE AGENCY'S AUTHORITATIVE PEER-REVIEWED DETERMINATIONS OF THE HEALTH EFFECTS OF CHEMICALS

Five of the 10 chemicals – TCE, MC, CTC, PERC and 1,4-dioxane – have been assessed under the EPA Integrated Risk Information System (IRIS). The IRIS process is the Agency's authoritative mechanism for reviewing available studies, characterizing the health effects of chemicals and identifying concentrations below which these chemicals are not likely to cause adverse effects. IRIS assessments typically reflect

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weather events, heat waves, spread of infectious diseases and detrimental impacts on air and water quality are having impacts on our health." https://www.epa.gov/climate-research/human-health-and-climate-change-research (accessed 9-18-17).

[22] Trichloroethylene (TCE); Regulation of Use in Vapor Degreasing under TSCA Section 6(a), 82 Fed. Reg. 7432 (Jan. 19, 2017); Trichloroethylene; Regulation of Certain Uses under TSCA § 6(a), 81 Fed. Reg. 91592 (Dec. 16, 2016) and Methylene Chloride and N-Methylpyrrolidone; Regulation of Certain Uses under TSCA Section 6(a), 82 Fed. Reg. 7464 (Jan. 19, 2017).

[23] See, e.g., EPA. *Scope of the Risk Evaluation for Trichloroethylene,* June 2017, at 33.

years of work by EPA scientists, multiple rounds of public comment, inter and intra-agency consultation, and extensive peer review, often by the Agency's independent Science Advisory Board (SAB) or the National Academy of Sciences (NAS).

Where EPA is conducting a TSCA risk evaluation of a chemical that has already been assessed under IRIS, the conclusions of the IRIS assessment should be presumed to be applicable to the TSCA evaluation as a definitive statement by the Agency of the best available science. To revisit IRIS findings would be inefficient and resource-intensive at a time when the Agency is struggling with workforce and budget reductions. It would also make the three-year statutory deadline for completing risk evaluations even more challenging by greatly expanding the scope of EPA's work effort. Most significantly, reopening IRIS findings would prolong scientific uncertainty on issues that have been addressed and resolved through an authoritative, transparent and inclusive EPA process. Like other Agency actions, IRIS assessments often give rise to differences of opinion and some stakeholders may be disappointed by the outcome. But this does not mean that EPA should reinvent the wheel and provide another bite at the apple on scientific determinations that have been made after thorough deliberation and a robust process.

In sum, the problem formulation documents on the 10 chemicals should make clear that EPA's risk evaluations will rely on previous IRIS assessments in determining health effects that those assessments address.

VIII. IN EVALUATING WORKPLACE RISKS, EPA SHOULD RECOGNIZE THE UNEVEN USE AND EFFECTIVENESS OF ENGINEERING CONTROLS, LABELING AND PERSONAL PROTECTIVE EQUIPMENT IN PREVENTING OCCUPATIONAL EXPOSURE

Several scoping documents indicate that, in its approach to occupational exposure analysis, EPA will "[c]onsider and incorporate applicable engineering controls and/or personal protective equipment into exposure scenarios."[24] These measures are certainly relevant factors in analyzing occupational exposures. However, it is essential that EPA not presume that they will be effective in preventing exposure in all workplaces and for all employees. In many cases, they may in fact provide limited protection, particularly for short-term poorly trained workers in small shops and workers whose English language skills are challenged.

In its proposed section 6(a) rules for TCE, MC and NMP, EPA explained at some length why label warnings and instructions are not uniformly read, comprehended or followed and thus provide limited protection. This was not a mere opinion on EPA's part but the result of an examination of nearly fifty studies.[25] Based on this review, EPA's conclusions as described in its initial TCE rulemaking were as follows:

> "The Agency determined that warning labels and instructions alone could not mitigate the risks to the extent necessary so that TCE no longer presents the identified unreasonable risks to users. The Agency based this determination on an analysis of 48 relevant studies or meta-analyses, which found that consumers and professionals do not consistently pay attention to

[24] See, for example, US EPA (2017). Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster. Pg. 45

[25] OPPT summarized these studies in a paper entitled *The Effectiveness of Labeling on Hazardous Chemicals and Other Products* (March 2016)(Ref. 33 in rulemaking docket).

labels; consumers and professional users often do not understand label information; consumers and professional users often base a decision to follow label information on previous experience and perceptions of risk; even if consumers and professional users have noticed, read, understood, and believed the information on a hazardous chemical product label, they may not be motivated to follow the label information, instructions, or warnings; and consumers and professional users have varying behavioral responses to warning labels, as shown by mixed results in studies."[26]

In the TCE vapor degreasing proposal, EPA further concluded that comprehension of warnings would be unusually challenging because of the complexity of the information conveyed:

> "EPA found that presenting information about TCE on a label would not adequately address the identified unreasonable risks because the nature of the information the user would need to read, understand, and act upon is extremely complex. It would be challenging to most users to follow or convey the complex product label instructions required to explain how to reduce exposures to the extremely low levels needed to minimize the risk from TCE. Rather than a simple message, the label would need to explain a variety of inter-related factors, including but not limited to the use of local exhaust ventilation, respirators and assigned protection factor for the user and bystanders, and time periods during pregnancy with susceptibility of the developing fetus to acute developmental effects, as well as effects to bystanders. *It is unlikely that label language changes for this use will result in widespread, consistent, and successful adoption of risk reduction measures by users and owners.*[27]

Similarly, EPA cautioned that "there are many documented limitations to successful implementation of respirators", including these well-known problems: [28]

> "Not all workers can wear respirators. Individuals with impaired lung function, due to asthma, emphysema, or chronic obstructive pulmonary disease for example, may be physically unable to wear a respirator. Determination of adequate fit and annual fit testing is required for a tight fitting full-face piece respirator to provide the required protection. Also, difficulties associated with selection, fit, and use often render them ineffective in actual application, preventing the assurance of consistent and reliable protection, regardless of the assigned capabilities of the respirator. Individuals who cannot get a good face piece fit, including those individuals whose beards or sideburns interfere with the face piece seal, would be unable to wear tight fitting respirators. In addition, respirators may also present communication problems, vision problems, worker fatigue and reduced work efficiency (63 FR 1156, January 8, 1998). According to OSHA, 'improperly selected respirators may afford no protection at all (for example, use of a dust mask against airborne vapors), may be so uncomfortable as to be intolerable to the wearer, or may hinder vision, communication, hearing, or movement and thus pose a risk to the wearer's safety or health. (63 FR 1189-1190).'"

EPA based these conclusions on expert analyses by OSHA, which has extensive experience with respirators under its workplace standards.

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[26] 81 FR at 91601.
[27] 82 FR 7441 (emphasis added)
[28] 82 FR 7445

The problem formulation documents should explicitly recognize that industrial hygiene controls do not necessarily provide reliable and effective protection from exposure and that the adequacy of these controls needs to be examined on a case-by-case basis in the context of the specific establishments where the chemical is used, the makeup of the worker population in these establishments and the diligence of employers in implementing workplace controls. During problem formulation, EPA should elaborate on how these considerations will be applied for the 10 chemicals.

More generally, when considering occupational exposures, EPA needs to recognize and account for differences in levels of exposure, workplace practices and susceptibility that result in significant gradations in risk, even within a single workplace. In workplaces where chemicals and chemical products are used, exposures typically occur most intensely among a highly exposed subgroup, rather than uniformly across the population of workers. In a vehicle repair shop, for example, chemical-intensive tasks on brakes, engines, and drive-train components are performed by a subset of workers who experience high levels of exposure to aerosolized degreasing solvents, whereas other workers in the same shop who perform diagnostic or electrical work, for example, experience little or no exposure to these solvents. To effectively characterize the "conditions of use" among workers, EPA must account for the levels and duration of exposure—and therefore risk—that occurs within highly exposed subgroups as a consequence of actual workplace conditions, rather than relying on an "average" estimated exposure across a population of workers, based on an assumption of "intended" use.

IX. EPA SHOULD NOT EXCLUDE FROM THE 1,4-DIOXANE EVALUATION ITS PRODUCTION AS A BYPRODUCT OR IMPURITY, WHICH IS A SIGNIFICANT SOURCE OF CONTAMINATION OF WATER SOURCES

The scoping document for 1,4-dioxane takes the unusual approach of precluding any consideration of this substance's manufacture as a byproduct or impurity in EPA's risk evaluation:

> "In the case of 1,4-dioxane, EPA anticipates that production of 1,4-dioxane as a by-product from ethoxylation of other chemicals and presence as a contaminant in industrial, commercial and consumer products will be excluded from the scope of the risk evaluation. These 1,4-dioxane activities will be considered in the scope of the risk evaluation for ethoxylated chemicals. EPA believes its regulatory tools under TSCA section 6(a) are better suited to addressing any unreasonable risks that might arise from these activities through regulation of the activities that generate 1,4-dioxane as an impurity or cause it to be present as a contaminant than they are to addressing them through direct regulation of 1,4-dioxane"[29]

This is a deeply flawed approach that will weaken the 1,4-dioxane risk evaluation and result in inadequate risk reduction during any subsequent rulemaking under section 6(a).

1,4-dioxane is a probable carcinogen that has contaminated drinking water and groundwater in multiple parts of the country, eliciting expressions of concern from many public officials and communities. A recent analysis of data from EPA-mandated monitoring indicates that water supplies for more than 7

[29] Scope of the Risk Evaluation for 1,4-Dioxane, at 8 (June 2017)

million Americans in 27 states contain 1,4-dioxane at levels above those that EPA and other agencies believe present an acceptable cancer risk.[30]

1,4-dioxane's presence in drinking water and groundwater is linked to several pathways of release into the environment. In addition to its manufacture as a chemical product, 1,4-dioxane is a byproduct of plastic production and other chemical manufacturing processes utilizing ethoxylation. Due to its production as a byproduct, it is present as an impurity in several industrial, commercial and consumer products. 1,4-dioxane often is found in the wastewater discharged by industrial facilities and POTWs. Its presence in wastewater is likely attributable not only to intentional production and use activities but to the use and disposal of products in which it is present as an impurity.

If 1,4-dioxane's manufacture as a byproduct and presence in products and waste streams as an impurity are excluded from EPA's risk evaluation, it will have no basis for accounting for these sources of environmental release and will be unable to characterize their contribution to levels of the chemical found in drinking water, surface water and ground water. This will make its assessment of the extent and causes of water contamination incomplete and undermine its ability to conduct an informed evaluation of the options for reducing contamination and risk. Any action it later decides to take under section 6 will thus be based on inadequate information and analysis and, as a result, may be ineffective and under-protective.

Manufacture as a byproduct is plainly within the definition of "conditions of use" in section 3(4) of TSCA. There is no basis in this provision or other parts of the law for differentiating between manufacture as a byproduct and purposeful production and including one in a risk evaluation but excluding the other. And in this instance, there's no evidence (and EPA does not claim) that exposure to and release of 1,4-dioxane as a byproduct and impurity are inconsequential from a risk standpoint.[31]

While EPA suggests that it might be more efficient or effective to address byproduct production of 1,4-dioxane in a separate section 6(a) rulemaking for ethoxylated chemicals, this seems far-fetched. If EPA assesses the contribution of these chemicals to 1,4-dioxane water contamination in the current risk evaluation, it will have a sound basis to regulate their production and use under section 6(a) if they are found to present an unreasonable risk of injury.[32] Otherwise, there is no telling when EPA might mitigate water contamination resulting from byproduct production of 1,4-dioxane production. Thus far, EPA has offered no indication when, if ever, it will make a high-priority designation for ethoxylated chemicals and assess their contribution to the presence of 1,4-dioxane in the environment.

We recommend that during problem formulation, EPA add 1,4-dioxane production as a byproduct and impurity to the scope of its risk evaluation.

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[30] Environmental Working Group, HIDDEN CARCINOGEN TAINTS TAP WATER, CONSUMER PRODUCTS NATIONWIDE (September 2017).

[31] Under our interpretation of section 6(b), EPA could not exclude a condition of use from the risk evaluation scope based on low risk in any event.

[32] Section 6(a) does not limit EPA to regulating purposeful production of a chemical subject to a risk evaluation. It can regulate production by other means so long as it has been assessed in that evaluation and found to present an unreasonable risk.

X. BASED ON THE GENERAL PRINCIPLES OUTLINED ABOVE AND OTHER GAPS IN ITS SCOPING DOCUMENTS, EPA SHOULD AUGMENT THESE DOCUMENTS IN SEVERAL SPECIFIC RESPECTS DURING PROBLEM FORMULATION

Applying the general approaches outlined in these comments and in light of several omissions we identified in individual scoping documents, we recommend that EPA bolster those documents during problem formulation as follows:

1-Bromopropane (nPB)

- In our initial comments to EPA, we specifically identified nPB as being imported by companies whose primary business is supplying the cosmetics industry.[33] While the EPA has noted that authorities such as the State of California have included nPB on lists of chemicals banned in cosmetics, the potential for nPB directly or indirectly (through residues remaining from cleaning manufacturing equipment) to be present in cosmetic products is not addressed as a potential use for further assessment.
- As discussed in detail in Part V of these comments, EPA failed to address the ozone depletion potential of nPB.
- While the scoping document includes references to those exposed to nPB from use of the chemical in consumer products, as well as those co-located with dry cleaning facilities utilizing the chemical, it does not clearly identify people who may be further exposed from chemical residuals, such as those wearing clothing cleaned with nPB or their children. This pathway is not discussed, even though the scoping document for PERC includes it from the similar use of PERC in dry cleaning.

Asbestos

- EPA's scoping document claims that public comments were not received on various imported asbestos containing products available in the United States: "Products available from several online retailers and distributers include brake blocks, aftermarket friction products, roof and non-roof coatings, and gaskets, most of which are imported. No public comments were received regarding these uses." However, we submitted detailed comments highlighting all of these items and more, including other building products. [34]
- EPA's failure to include a lengthy list of legacy uses, as further discussed in Part IV of these comments, is especially problematic for asbestos which was extensively sold and distributed and remains widely present and in use in our buildings and cities.
- The recycling of legacy materials, notably asphalt shingles containing asbestos, is a unique and ongoing use of the substance, and in particular is worthy of additional consideration by the EPA, as discussed in our initial comments.[35]

[33] EPA-HQ-OPPT-2016-0741-0027 at PDF Pages 25, 27, 31.
[34] EPA-HQ-OPPT-2016-0736-0064 at PDF Pages 19, 25-27
[35] EPA-HQ-OPPT-2016-0736-0064 at PDF Pages 21-22

- There is evidence that asbestos has been present in significant levels in some talc products as the result of colocation of asbestos and talc deposits, as we discussed in our initial comments.[36] This use and ongoing exposure are not addressed in the scoping document.

- The scoping document fails to look at the risks of exposure to those who are upstream to the process of utilizing asbestos in chlor-alkali processing. This would include miners and packaging workers (who, while likely abroad, are still being exposed as a result of the substance's uses in the US considered by the EPA), as well as transportation workers, first responders, and community members who may be exposed in the shipment and transfer of asbestos to the chlor-alkali facilities.

- The absence in the scoping document of total import volumes for asbestos is troubling because it deprives the public of an understanding of the aggregate quantities of asbestos present in the US. In fact, the Asbestos Disease Awareness Organization, along with the Environmental Working Group, released a statement on September 19 that, based on data from the Department of Commerce and US International Trade Commission, 705 metric tons of raw asbestos were imported in 2016, compared to 343 metric tons in 2015. This significant increase in imports is important information that should be given prominence in the problem formulation document for asbestos.

Carbon Tetrachloride (CTC)

- As discussed in detail in Part V of these comments, EPA failed to address the ozone depletion potential and global warming potential of CTC in its scoping document. This is particularly problematic for CTC, as its use as a feedstock or intermediary was exempted from the Montreal Protocol on the false assumption that CTC production would be phased out. In actuality, CTC production is poised for an increase due to its use in HFO manufacture, as we discussed on our initial comments.[37]

- As discussed in detail in Part III of these comments, EPA failed to describe with any specificity how it will look at aggregate and cumulative exposures. In the CTC scoping document, EPA seems to specifically discredit the need for this consideration. The Agency highlights the fact that some individuals may be exposed to CTC through vapor intrusion of ground sources of CTC into their home, but then states that, ". . . this route is not likely to be significant given the agency's identified conditions of use . . ." Clearly, whether the CTC inhaled by a resident is from the vapor intrusion or from an adhesive product, they face potential health risks from it. The Agency must consider all uses and sources of exposure in the risk evaluation in order to accurately assess the human health risk and fulfill its statutory obligations.

Cyclic Aliphatic Bromides Cluster (HBCD)

- As detailed in Part IV of these comments, EPA must not exclude the ongoing use and disposal from past introduction of HBCD in a variety of products. Significant exposures will continue to occur as products incorporating HBCD move through their lifecycle, and these exposures must be considered in the risk evaluation.

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[36] EPA-HQ-OPPT-2016-0736-0064 at PDF Pages 18-19

[37] EPA-HQ-OPPT-2016-0733-0023 at PDF pages 4-5, 19

N-Methylpyrrolidone (NMP)

- As we documented in our initial comments to the EPA, NMP has been used in the manufacturing of coating for the insides of aluminum spray cans.[38] Even products not including deliberate addition of NMP may therefore be contaminated with NMP, and this exposure pathway should be considered by the Agency.

- As detailed in Part II of these comments, EPA failed to provide specifics on susceptible subpopulations. While the Agency acknowledges that reproductive effects are to be assessed, considering the well-documented reproductive toxicity of NMP, the Agency needs to better detail how the risks to women of childbearing age will be addressed.

Methylene Chloride (MC)

- While the scoping document includes a use categorization for "other consumer products" including novelty "Drinking Bird" items, we identified an additional item,[39] a "Novelty Christmas Bubbling Night Light" labeled as containing MC but not previously included in EPA's "Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: Methylene Chloride." These consumer-oriented uses that are attractive to children illustrate the need to be comprehensive in the determination of "reasonably foreseeable" uses.

XI. EPA MAY NOT PREJUDGE THE ABSENCE OF ADVERSE EFFECTS FOR PARTICULAR END-POINTS AT THE SCOPING STAGE AND SHOULD DEFER SUCH CONCLUSIONS UNTIL THE SYSTEMATIC REVIEW STAGE OF ITS RISK EVALUATION

In some scoping documents, EPA has decided that the subject chemical does not raise concerns for particular endpoints and, therefore, it will not address these end-points in its risk evaluation. Examples are given in the table below where EPA concludes that HBCD, NMP and pigment violet 29 are not genotoxic:

Chemical	Example Text from EPA Scoping Document
HBCD	"Available data suggest that HBCD is not genotoxic. Existing assessments have also concluded, based on genotoxicity information and a limited lifetime study, that HBCD is not carcinogenic (NICNAS, 2012; EINECS, 2008; TemaNord, 2008; OECD, 2007). Unless new information indicates otherwise, EPA does not expect to conduct additional in-depth analysis of genotoxicity or cancer hazards in the risk evaluation of HBCD at this time."[40]
NMP	"NMP is not mutagenic, based on results from bacterial and mammalian *in vitro* tests and *in vivo* systems and is not considered to be carcinogenic (RIVM, 2013; OECD, 2007; WHO, 2001). Unless new information indicates otherwise, EPA does not expect to conduct additional in-depth analysis of genotoxicity and cancer hazards in the NMP risk evaluation."[41]

[38] EPA-HQ-OPPT-2016-0743-0031 at PDF page 18
[39] https://www.amazon.com/Bubble-Nightlight-Novelty-Christmas-Bubbling/dp/B00PV61HXC/
[40] EPA, *Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster, June 2017, at.* 36
[41] EPA, *Scope of the Risk Evaluation for N-Methylpyrrolidone,* June 2017, *at* 36

Pigment violet 29	"Testing for carcinogenicity of Pigment Violet 29 has not been conducted. However, negative genotoxicity results, structure-activity considerations and the expectation of negligible absorption and uptake of Pigment Violet 29 (based on very low solubility), indicate carcinogenicity of Pigment Violet 29 is unlikely. Unless new information indicates otherwise, EPA does not expect to conduct additional, in-depth analyses of genotoxicity and cancer hazards in the risk evaluation of Pigment Violet 29."[42]

EPA cannot reach such definitive conclusions at the scoping stage. The required course under the law is to proceed with a systematic review of the relevant data (a process that EPA strongly endorses) and withhold any conclusions about particular end-points until this review is complete.

In the case of HBCD, for example, a more thorough review would reveal two recent studies indicating carcinogenic potential. One suggests that HBCD could "enhance progression of prostate cancer by modulating growth and migration of LNCaP prostate cells,"[43] and the other concludes the genotoxicity of HBCD is dose-dependent and related to DNA repair.[44] These new studies are examples of the need for EPA to assure that it has fully considered all the available data through the systematic review process in order to avoid premature and possibly incorrect decisions to drop particular end-points at the scoping stage.

XII. PROBLEM FORMULATIONS SHOULD HIGHLIGHT ASPECTS OF USE AND EXPOSURE WHERE AVAILABLE INFORMATION IS INSUFFICIENT AND REQUEST OR REQUIRE SUBMISSION OF THIS INFORMATION BY INDUSTRY

Our own research on the 10 chemicals and the scoping documents themselves confirm that there are significant gaps in the use and exposure information available to EPA and that they will weaken the quality of EPA's risk evaluations unless filled. Although the timeframe for completing risk evaluations is compressed, there is still a window for augmenting the information-base used to conduct them. To take advantage of this opportunity, EPA should include in each problem formulation document a description of information on use and exposure that is lacking and a request that industry and other interested parties submit or obtain that information as expeditiously as possible.

EPA should also signal its readiness to use its mandatory information collection authorities under TSCA to fill data-gaps where voluntary submissions are not timely or adequate. The LCSA expands these authorities and streamlines the process for exercising them, removing the barriers to information development that hamstrung EPA under the old law. For example, section 4 now authorizes EPA to issue orders where necessary to "perform a risk evaluation." Such orders can be used to require industry to develop new information on the frequency, levels and duration of exposure for a chemical's conditions of use. Alternatively, EPA can use its subpoena authority under section 11 to obtain such information that already exists but has not been provided to EPA. EPA should specify in the problem formulation document its roadmap and timetable for filling data gaps using these authorities.

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[42] EPA, *Scope of the Risk Evaluation for Pigment Violet 29*, June 2017, at 29.

[43] Seung-Hee Kim, et al, 2016. Influence of hexabromocyclododecane and 4-nonylphenol on the regulation of cell growth, apoptosis and migration in prostatic cancer cells. Toxicology in Vitro. 32:240-247. April 2016.

[44] Rui Jing Li, et al. Hexabromocyclododecane-induced Genotoxicity in Cultured Human Breast Cells through DNA Damage. Letter to Editor. Biomedical and Environmental Sciences. 30(4): 296-300.

Where the database available for a risk evaluation is incomplete, it is critically important that EPA not equate the absence of data with the absence of risk. For example, if EPA lacks data to assess a chemical's carcinogenicity, its risk evaluation needs to clearly state that cancer risk has not been addressed, that the chemical may or may not present such a risk, and that this end-point is outside the scope of its evaluation because of the absence of data. EPA should make the same disclaimers for conditions of use that cannot be adequately characterized, even by using default assumptions or extrapolation methods, because basic information about the nature of the use and scope and extent of exposure is unavailable.

XIII. EPA NEEDS TO LIMIT REDACTION FROM SCOPING AND PROBLEM FORMULATION DOCUMENTS OF CRITICAL INFORMATION CLAIMED CBI SO THAT TRANSPARENCY AND PUBLIC PARTICIPATION IN THE RISK EVALUATION PROCESS ARE NOT IMPAIRED

The scoping documents omit critical exposure and use information that has been claimed as confidential business information (CBI) that must be withheld from disclosure under TSCA. In some cases, the information is as basic as the total volume of the chemical manufactured and imported in the US. For example, the scoping documents fail to provide total manufacture/import volumes for asbestos, HBCD and pigment violet 29. Not only is this information obtainable in the public domain but it is fundamental to public understanding of the risks posed by these chemicals and, therefore, to informed public participation in the risk evaluation process.[45]

During problem formulation, EPA should make a concerted effort to limit the redaction of CBI-claimed production, use and exposure data that are essential for the transparency of the risk evaluation process. Several tools can be used for this purpose.

First, section 14(b)(3) of TSCA declares that "information not protected from disclosure" includes:

> "any general information describing the manufacturing volumes, expressed as specific aggregated volumes or . . . expressed in ranges."
>
> "a general description of a process used in the manufacture or processing and industrial, commercial or consumer functions and uses of a chemical, substance, mixture or article containing a chemical substance or mixture . . ."

This provision compels the disclosure of much of the information in scoping documents claimed CBI.

Alternatively, section 14(d)(7) provides that the Administrator may disclose information otherwise warranting CBI protection if he or she "determines that disclosure is relevant in a proceeding under this Act." The risk evaluations that EPA is conducting on the 10 chemicals under section 6(b)(2)(A) of TSCA represent a "proceeding" under TSCA. Information submitted by industry on the 10 chemicals is plainly "relevant" to these evaluations because it will inform how EPA assesses exposures and related risks

[45] For asbestos, SCHF and Environmental Health Strategy Center were able to use US government data accessible through the Panjiva database to determine annual asbestos imports over an extended period. As noted above, a more recent analysis of import data by the Asbestos Disease Awareness Organization shows that asbestos imports doubled in 2016, a startling finding that should be central to EPA's risk evaluation because of its implications for exposure to asbestos in the US.

associated with manufacture, processing and downstream commercial and consumer use. Thus, EPA can and should decide to disclose all information on the 10 chemicals notwithstanding any CBI claims.

Finally, to the extent these grounds for disclosure do not apply, EPA should use its authority under section 14(f)(1)(C) to require immediate substantiation of CBI claims for information for which "disclosure would be important to assist the Administrator in conducting risk evaluations . . . under section 6." This provision should be applied broadly to accomplish disclosure of all information that would be of value to the public in commenting on risk evaluations.

CONCLUSION

Our groups appreciate the opportunity to comment on the 10 scoping documents and look forward to continued dialogue with the Agency as it develops problem formulation documents and proceeds with risk evaluations on the 10 chemicals.

If you have any questions, please contact SCHF counsel, Bob Sussman, at bobsussman1@comcast.net or 202-716-0118.

Respectfully submitted,

Elizabeth Hitchcock, Government Affairs Director, Safer Chemicals Healthy Families

Eve Gartner, Staff Attorney, Earthjustice

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Daniel Rosenberg, Senior Attorney, Natural Resources Defense Council

Laurie Valeriano, Executive Director, Toxic-Free Future

Linda Reinstein, President, Asbestos Disease Awareness Organization

September 19, 2017

Message

From: Faeth, Lisa [Faeth.Lisa@epa.gov]
Sent: 6/5/2018 3:11:42 PM
To: Askinazi, Valerie [Askinazi.Valerie@epa.gov]; Barkas, Jessica [barkas.jessica@epa.gov]; Beck, Nancy [Beck.Nancy@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Blair, Susanna [Blair.Susanna@epa.gov]; Blunck, Christopher [Blunck.Chris@epa.gov]; Brown, Sam [Brown.Sam@epa.gov]; Buster, Pamela [Buster.Pamela@epa.gov]; Canavan, Sheila [Canavan.Sheila@epa.gov]; Caraballo, Mario [Caraballo.Mario@epa.gov]; Carroll, Megan [Carroll.Megan@epa.gov]; Cherepy, Andrea [Cherepy.Andrea@epa.gov]; Christian, Myrta [Christian.Myrta@epa.gov]; Corado, Ana [Corado.Ana@epa.gov]; Davies, Clive [Davies.Clive@epa.gov]; DeDora, Caroline [DeDora.Caroline@epa.gov]; Devito, Steve [Devito.Steve@epa.gov]; Doa, Maria [Doa.Maria@epa.gov]; Drewes, Scott [Drewes.Scott@epa.gov]; Dunton, Cheryl [Dunton.Cheryl@epa.gov]; Ebzery, Joan [Ebzery.Joan@epa.gov]; Edelstein, Rebecca [Edelstein.Rebecca@epa.gov]; Edmonds, Marc [Edmonds.Marc@epa.gov]; Eglsaer, Kristie [Eglsaer.Kristie@epa.gov]; Elwood, Holly [Elwood.Holly@epa.gov]; Faeth, Lisa [Faeth.Lisa@epa.gov]; Farquharson, Chenise [Farquharson.Chenise@epa.gov]; Fehrenbacher, Cathy [Fehrenbacher.Cathy@epa.gov]; Feustel, Ingrid [feustel.ingrid@epa.gov]; Frank, Donald [Frank.Donald@epa.gov]; Gibson, Hugh [Gibson.Hugh@epa.gov]; Gimlin, Peter [Gimlin.Peter@epa.gov]; Gorder, Chris [Gorder.Chris@epa.gov]; Gordon, Brittney [Gordon.Brittney@epa.gov]; Grant, Brian [Grant.Brian@epa.gov]; Gray, Shawna [Gray.Shawna@epa.gov]; Groeneveld, Thomas [Groeneveld.Thomas@epa.gov]; Guthrie, Christina [Guthrie.Christina@epa.gov]; Helfgott, Daniel [Helfgott.Daniel@epa.gov]; Henry, Tala [Henry.Tala@epa.gov]; Kapust, Edna [Kapust.Edna@epa.gov]; Kemme, Sara [kemme.sara@epa.gov]; Koch, Erin [Koch.Erin@epa.gov]; Krasnic, Toni [krasnic.toni@epa.gov]; Lavoie, Emma [Lavoie.Emma@epa.gov]; Leczynski, Barbara [leczynski.barbara@epa.gov]; Lee, Mari [Lee.Mari@epa.gov]; Lee, Virginia [Lee.Virginia@epa.gov]; Leopard, Matthew (OEI) [Leopard.Matthew@epa.gov]; Liva, Aakruti [Liva.Aakruti@epa.gov]; Lobar, Bryan [Lobar.Bryan@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Menasche, Claudia [Menasche.Claudia@epa.gov]; Morris, Jeff [Morris.Jeff@epa.gov]; Moss, Kenneth [Moss.Kenneth@epa.gov]; Mottley, Tanya [Mottley.Tanya@epa.gov]; Moyer, Adam [moyer.adam@epa.gov]; Myers, Irina [Myers.Irina@epa.gov]; Myrick, Pamela [Myrick.Pamela@epa.gov]; Nazef, Laura [Nazef.Laura@epa.gov]; Ortiz, Julia [Ortiz.Julia@epa.gov]; Owen, Elise [Owen.Elise@epa.gov]; Parsons, Doug [Parsons.Douglas@epa.gov]; Passe, Loraine [Passe.Loraine@epa.gov]; Pierce, Alison [Pierce.Alison@epa.gov]; Pratt, Johnk [Pratt.Johnk@epa.gov]; Price, Michelle [Price.Michelle@epa.gov]; Reese, Recie [Reese.Recie@epa.gov]; Reisman, Larry [Reisman.Larry@epa.gov]; Rice, Cody [Rice.Cody@epa.gov]; Richardson, Vickie [Richardson.Vickie@epa.gov]; Ross, Philip [Ross.Philip@epa.gov]; Sadowsky, Don [Sadowsky.Don@epa.gov]; Santacroce, Jeffrey [Santacroce.Jeffrey@epa.gov]; Saxton, Dion [Saxton.Dion@epa.gov]; Scarano, Louis [Scarano.Louis@epa.gov]; Scheifele, Hans [Scheifele.Hans@epa.gov]; Schmit, Ryan [schmit.ryan@epa.gov]; Schweer, Greg [Schweer.Greg@epa.gov]; Selby-Mohamadu, Yvette [Selby-Mohamadu.Yvette@epa.gov]; Seltzer, Mark [Seltzer.Mark@epa.gov]; Sheehan, Eileen [Sheehan.Eileen@epa.gov]; Sherlock, Scott [Sherlock.Scott@epa.gov]; Simons, Andrew [Simons.Andrew@epa.gov]; Sirmons, Chandler [Sirmons.Chandler@epa.gov]; Slotnick, Sue [Slotnick.Sue@epa.gov]; Smith, David G. [Smith.DavidG@epa.gov]; Stedeford, Todd [Stedeford.Todd@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Symmes, Brian [Symmes.Brian@epa.gov]; Tanner, Barbara [Tanner.Barbara@epa.gov]; Thompson, Tony [Thompson.Tony@epa.gov]; Tierney, Meghan [Tierney.Meghan@epa.gov]; Tillman, Thomas [Tillman.Thomas@epa.gov]; Tomassoni, Guy [Tomassoni.Guy@epa.gov]; Tran, Chi [Tran.Chi@epa.gov]; Vendinello, Lynn [Vendinello.Lynn@epa.gov]; Wallace, Ryan [Wallace.Ryan@epa.gov]; Wheeler, Cindy [Wheeler.Cindy@epa.gov]; Widawsky, David [Widawsky.David@epa.gov]; Williams, Aresia [Williams.Aresia@epa.gov]; Williams, Bridget [Williams.Bridget@epa.gov]; Williamson, Tracy [Williamson.Tracy@epa.gov]; Wills, Jennifer [Wills.Jennifer@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Wolf, Joel [Wolf.Joel@epa.gov]; Wright, Tracy [Wright.Tracy@epa.gov]; Yowell, John [yowell.john@epa.gov]
Subject: News Articles (For EPA Distribution Only)

BNA DAILY ENVIRONMENT REPORT ARTICLES

Chemical Board Closure Threat Found to Repel Job-Seekers: Audit

By Sam Pearson

Posted June 4, 2018, 4:03 PM

The Trump administration's push to eliminate the Chemical Safety Board is preventing the agency from attracting and keeping staff, and board members too often pursue individual agendas in ways that harm morale, the EPA's inspector general found June 4.

EPA Aide Helped Pruitt Arrange Trips, Find Housing, Buy Mattress (1)

By Jennifer A. Dlouhy and Billy House

Posted June 4, 2018, 11:06 AMUpdated June 4, 2018, 12:47 PM

A top EPA aide helped agency chief Scott Pruitt try to buy a used mattress from the Trump International Hotel, one of several personal tasks she conducted for the administrator whose sleeping arrangements have already prompted investigations.

Going Greener Can Get You Cheaper Loans at This Dutch Bank

By Anna Hirtenstein

Posted June 4, 2018, 10:51 AM

Going green is more than just a question of morality at ING Groep NV. It can also result in cheaper funds.

INSIDEEPA.COM ARTICLES

Eying 2018 Deadline, EPA Taps New Division Heads For Reorganized OPPT

Leaders of EPA's toxics office have selected many of the new division directors for the office's planned overhaul and are proceeding with additional management selections as part of a plan to complete the reorganization -- which aims to better implement the revised Toxic Substances Control Act (TSCA) -- by year's end.

EPA Narrows Scope Of First 10 TSCA Assessments, Drawing Criticisms

EPA is further narrowing its approach for assessing the risks of the first 10 "existing" chemicals it is reviewing for possible regulation under the new Toxic Substances Control Act (TSCA), issuing problem formulation documents that preclude consideration of risks that other agency programs are already addressing.

EPA Strengthens Internal Review Of Science Rule As SAB Seeks Scrutiny

Top EPA officials have decided to strengthen the internal agency review of Administrator Scott Pruitt's controversial proposed rule requiring the use of publicly available research to justify rules just as the agency's Science Advisory Board (SAB) voted unanimously to review the measure amid broad criticisms.

Lowe's To Cease Sales Of Paint Strippers Containing Methylene Chloride

Lowe's hardware store chain is planning to phase out paint strippers containing methylene chloride and N-methylpyrrolidone (NMP) from its global product selection by the end of the year, an announcement that comes days after EPA reversed course and pledged to complete a landmark Obama-era rule regulating similar uses of the chemical.

EPA Doubts EDF's Standing To Challenge TSCA Inventory Update Rule

EPA is urging a federal appellate court to reject a suit brought by Environmental Defense Fund (EDF) challenging its rule updating the inventory of existing chemicals that could be regulated under the new Toxic Substances Control Act (TSCA), charging the group lacks standing to sue because it will not be injured and that the update is "reasonable" and within the statute.

House Democrats Question Industry Influence In PFAS Report Delay

House Democrats are questioning whether Trump EPA appointees were swayed by the chemical industry last January, when they acted with Defense Department counterparts to stall a draft Agency for Toxic Substances and Disease Registry (ATSDR) study of four PFAS chemicals, including some risk estimates stricter than EPA's.

Obama-era Formaldehyde Emissions Rule Takes Effect, Winning Praise

Environmentalists and domestic producers are jointly touting the June 1 deadline for enforcing an Obama-era rule setting emissions standards for formaldehyde from wood products, a deadline they agreed to after environmentalists beat back an industry-backed Trump administration effort to delay the rule's implementation for an additional six months.

Once Concerned, ACC Now On Board With Pruitt's Science Rule Proposal

The American Chemistry Council (ACC) has become an enthusiastic supporter of Administrator Scott Pruitt's draft rule on science transparency at EPA, even as the group was initially concerned that the proposed rule -- and the Republican legislation on which it is based -- may not have adequately protected trade secrets.

GREENWIRE ARTICLES

Pruitt wanted 'old mattress' from Trump Hotel — aide

Kevin Bogardus, E&E News reporter

Published: Monday, June 4, 2018

EPA headquarters can be seen past a sign at Trump International Hotel in Washington. Hannah Northey/E&E News

Democrats on the House Oversight and Government Reform Committee released excerpts today of an interview with a top aide to Administrator Scott Pruitt, shedding more light on her housing search on behalf of the embattled EPA chief.

In a letter to Chairman Trey Gowdy (R-S.C.), ranking member Elijah Cummings (D-Md.) and Rep. Gerry Connolly (D-Va.) said EPA's Millan Hupp confirmed allegations she helped find a new apartment for Pruitt while revealing "significant new details" on the personal tasks she did for Pruitt, including using his credit card to book his personal flights and trying to secure a used mattress from the Trump International Hotel in Washington.

https://www.eenews.net/greenwire/2018/06/04/stories/1060083411

Lobbyist tied to Pruitt's condo represented more clients

Kevin Bogardus, E&E News reporter

Published: Monday, June 4, 2018

EPA Administrator Scott Pruitt rented this Capitol Hill condominium from the wife of a lobbyist whose clients lobbied EPA. Kevin Bogardus/E&E News

A lobbyist tied to a Capitol Hill condo that EPA Administrator Scott Pruitt rented part of last year had business with the agency on behalf of at least three clients.

Steven Hart, the former chairman of Williams & Jensen PLLC, had over the past year represented Smithfield Foods Inc., Coca-Cola Co., and the Financial Oversight and Management Board for Puerto Rico before EPA, according to several amended lobbying disclosure reports filed by the firm Friday.

In March, news broke that Pruitt had rented a condo from Hart's wife for $50 a night for part of 2017, with the subsequent controversy attracting scrutiny from lawmakers and the EPA inspector general.

https://www.eenews.net/greenwire/2018/06/04/stories/1060083425

APPROPRIATIONS

Committee to vote on Interior-EPA bill

Manuel Quiñones, E&E News reporter

Published: Monday, June 4, 2018

The House Appropriations Committee plans to vote this week on one of the most contentious spending measures of the year: legislation to fund EPA and the Interior Department.

The panel was supposed to have marked up the bill before the Memorial Day recess but postponed consideration until Wednesday morning.

The House Interior and Environment Appropriations Subcommittee approved the legislation in May. The measure was largely bipartisan, but Democrats grumbled about some riders and promised to pursue amendments (E&E Daily, May 16).

https://www.eenews.net/greenwire/2018/06/04/stories/1060083407

Nation bans plastic bags at retailers to protect coasts

Published: Monday, June 4, 2018

Chile will bar plastic bags at retail businesses, becoming the first nation in the Americas to do so.

The Chilean Congress approved the measure unanimously last week. Large businesses will have six months to get into compliance, while smaller outfits will get a two-year window.

The bill is an effort to protect the country's 4,000 miles of coasts. Nearly 80 local governments have already adopted some form of restriction on plastic bags, while a handful of coastal communities have banned them outright.

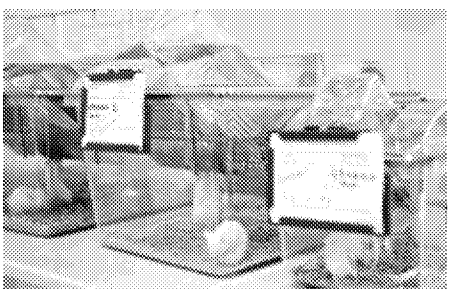
https://www.eenews.net/greenwire/2018/06/04/stories/1060083371

CHEMICAL WATCH ARTICLES

Ombudsman probes EU's slow adoption of non-animal tests

Over four million animals likely test subjects under REACH, NGO says

4 June 2018 / Europe, REACH, Test methods



The European ombudsman is investigating a complaint by NGO Cruelty Free International about the European Commission's "ongoing failure" to regularly update the list of alternatives to animal tests that can be used to assess the safety of chemicals under REACH.

In its complaint to the ombudsman last December, CFI argued that the long delays the Commission "routinely allows" for the inclusion of validated non-animal tests in the Test Method Regulation (TMR) constitute "maladministration".

As a consequence CFI claims it is likely that as many as four million animals have been used in tests to meet the 2018 deadline.

The overriding principle under REACH Article 13 is that animals can only be used as a last resort – the so-called three Rs (replacement, reduction and refinement). TMR is the regulatory step to bring a validated alternative into the legal system.

The Commission has a 'duty' to amend the TMR as soon as possible to advance the three Rs, CFI said

The Commission has a "duty" to amend the TMR as soon as possible to advance the three Rs, CFI said.

The time it should take to include a validated test method, it added, is about nine to 12 months. But, according to CFI, it is averaging four years. This includes a delay of between two and three years, following the OECD's acceptance of an alternative test.

One method was validated over 16 years ago and has yet to be included in the TMR, it said.

It asked the ombudsman to recommend that the Commission:

- removes the OECD stage from updating the TMR; and
- takes steps to significantly reduce the current delays.

The NGO is also challenging the Commission's position, set out in its reply to CFI in July last year, that updating the regulation "is not pivotal".

The Commission has until 31 July to respond to the ombudsman's request.

In July last year, the ombudsman dismissed a complaint by a UK-based animal rights NGO about the Commission's "misleading" approach to animal testing for cosmetics products. It concluded there was "no maladministration" on the part of Commission and Echa.

Four million animals

In a statement released shortly after the REACH 2018 deadline, CFI said its analysis has shown that 2.2 million animals have been used in experiments for REACH in ten years of the Regulation.

It added that the figure does not include animal tests that will be conducted for "tens of thousands more substances" registered by 31 May.

The Commission had previously set out a 'best case' estimate of 1.9 million animals that would be tested on under REACH by 2018 and a 'worst case' estimate of 3.9 million, CFI said. The latter figure, it added, is "likely to be exceeded".

"Before everyone starts patting themselves on the back about how the numbers of animals are less than expected, let's look at the facts," Katy Taylor, director of science and regulatory affairs at CFI said. "They are higher than the Commission's worst-case estimate. The Commission and the agency have let animals down, as well as the public who were promised that animal testing would be a 'last resort'."

Animal tests continue to be carried out in the EU even where validated alternatives exist, CFI said. It called for "appropriate sanctions" in such situations.

Furthermore, if the EU deems a test unnecessary, there is "little benefit" in carrying it out for a third country that has "more onerous" requirements to satisfy, for example to assess toxicity, it added.

Clelia Oziel

Reporter

Related Articles

- Watchdog rejects NGO complaint on cosmetics animal testing

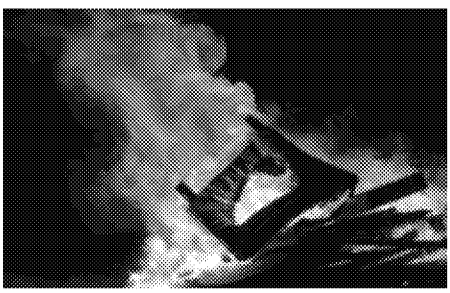
Further Information:

- Press release
- REACH Article 13

US CPSC plans to act on furniture flammability standard in 2019

Separate rule pending that could see flame retardants banned

4 June 2018 / Built environment, Halocarbons, United States



The US Consumer Products Safety Commission (CPSC) plans to make a decision in 2019 on whether to adopt California's Technical Bulletin (TB) 117-2013 as a national flammability standard for residential upholstered furniture, amid ongoing concern of the safety and necessity of added flame retardants.

The agency held a "technical meeting" on 16 May where stakeholders discussed furniture flammability hazard data, available technology and policy options.

According to the CPSC's regulatory agenda, staff are working with the National Fire Protection Association (NFPA), ASTM International and the California Bureau of Electronic and Appliance Repair, Home Furnishings and Thermal Insulation (Bearhfti), "to evaluate new provisions and improve the existing consensus standards related to upholstered furniture flammability."

The commission expects staff to present a briefing package recommending a course of action in fiscal year 2019, which begins this autumn.

The CPSC has been studying the issue for more than 15 years. It published a proposed rule in 2008 that would require upholstered furniture to have cigarette-resistant fabrics or flame-resistant barriers.

A *de facto* standard

In the absence of a federal standard, California's requirements have served as the *de facto* national standard for furniture flammability. Until a 2013 update, these had included an "open flame" test that effectively required the use of flame retardants.

The updated version of the California regulation, TB 117-2013, removed the open flame test and made more stringent a smoulder-resistance test. The result was a standard that could be met more readily without added flame retardants, and a marketplace shift away from their use.

A coalition of nine furniture industry groups petitioned the CPSC in 2014 to adopt the California standard, arguing that a national rule would improve fire safety and accelerate reductions in the use of flame retardant chemicals in furniture.

The North American Flame Retardant Alliance (Nafra) maintains that removing flame retardants from furniture eliminates important fire protection.

But the International Association of Fire Fighters sides with industry groups and NGOs that oppose use of the chemicals, arguing that burning furniture containing them is hazardous to firefighters.

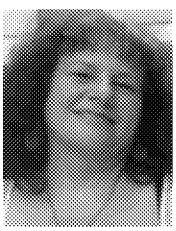
Flame retardant ban pending

Arguments surrounding the substances' toxicity were raised when the CPSC voted in 2017 to grant a separate petition calling for a wholesale ban on the use of organohalogen flame retardants (OFRs) in furniture and other categories of consumer products.

However, the 3-2 Democratic majority that took the vote is gone, and it is unclear how the agency will proceed with that rulemaking.

The commissioners ordered staff to convene a Chronic Hazard Advisory Panel (CHAP) to assess the risks of OFRs when they granted the petition. The current regulatory agenda says staff will complete a "scoping and feasibility study in cooperation with the National Academy of Sciences (NAS) of the direction given by the Commission." That study is due in April 2019.

Separately, the NFPA voted earlier this year to halt development of its own furniture flammability standard amid concern that flame retardants would be used to meet it, going against the current trend.



Julie Miller

Reporter

Related Articles

- California approves new upholstered furniture flammability standards
- US furniture industry calls for national flammability standard
- US CPSC investigates possible action against organohalogen flame retardants
- Senate confirms Baiocco for seat on US CPSC
- US body seeks nominees for flame retardant hazard assessment
- US body abandons plans for new flammability standard

Further Information:

- FDA regulatory agenda

EPA issues TSCA 'problem formulation' documents

Stakeholders remain divided over 'conditions of use' in risk evaluations

4 June 2018 / Substances of concern, TSCA, United States

The US EPA has released the 'problem formulation' documents of the first ten substances subject to risk evaluation under the recently reformed TSCA.

The documents refine the scope of the risk evaluations the agency will conduct on certain high-priority substances – which include asbestos, several chlorinated solvents, consumer products contaminant 1,4-dioxane and the flame retardant HBCD.

The documents serve as an interim step between last June's 'scoping documents' and the final risk evaluations, which must be completed by December 2019. They provide further clarity as to which 'conditions of use' will be evaluated for each substance.

According to the preamble of each problem formulation, the agency has removed from its risk evaluation those activities and exposure pathways it says "do not warrant inclusion in the risk evaluation". These include uses for which it has received insufficient information to demonstrate they actually are "intended, known, or reasonably foreseen" to take place.

To use its resources efficiently and to avoid duplicating efforts, it says it plans to "exercise its discretion ... to focus its analytical efforts on exposures that are likely to present the greatest concern and consequently merit a risk evaluation under TSCA," and exclude others.

Asbestos Snur, systematic review

Along with announcing release of the problem formulations, the EPA has issued a proposed significant new use rule (Snur) for asbestos.

It also published for public comment its systematic review approach document. This outlines how the EPA selects and reviews studies, and provides "continued transparency regarding how the agency plans to evaluate scientific information."

EPA Administrator Scott Pruitt said these actions provide "an opportunity to comment on how EPA plans to evaluate the ten chemicals undergoing risk evaluation, select studies, and use the best available science to ensure chemicals in the marketplace are safe".

Stakeholders remain divided

The American Chemistry Council (ACC) called the documents an "important milestone" in the new law's implementation.

The trade body said it will be analysing the documents to ensure they are "grounded in the best available science and the weight of the scientific evidence ... and are focused on the conditions of use that present the greatest potential risks so that the risk evaluations are protective and practical".

But the NGO community roundly criticised the formulations.

The Environmental Defense Fund said that by excluding certain conditions of use, the documents reflect a "seriously flawed approach" that will "severely underestimate" the risk the substances pose.

The agency will overlook "millions of pounds of toxic pollution", said Richard Denison, EDF's lead senior scientists. "EPA is both ignoring the law and endangering public health."

The Environmental Working Group added: "These woefully incomplete problem formulations signal the EPA's intent to discount human health risks to justify weak regulations of these chemicals."

Comments on the problem formulations and systematic review approach will be due within 45 days of their publications in the *Federal Register*. The asbestos Snur will be subject to a 60-day consultation.

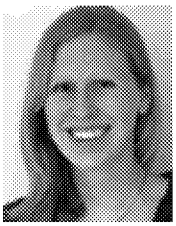
Conditions of use

How the EPA defines the 'conditions of use' that will be evaluated in a substance's risk evaluation has remained hotly contested since the Lautenberg Act reformed TSCA in June 2016.

Industry groups have argued that assessing every possible use of a substance is "unworkable". But consumer advocates have countered that omitting certain uses will incompletely capture the risk a substance poses – and correspondingly lead to insufficient risk management approaches.

The EPA's finalised 'framework rules' last June which narrowed the conditions of use to be evaluated in a risk evaluation, versus its original proposals.

A coalition of NGOs is now challenging this more limited scope in court.



Kelly Franklin

North America editor

Related Articles

- EPA names first ten chemicals for new TSCA evaluations
- US EPA issues final TSCA framework rules
- Stakeholders divided on defining conditions of use under TSCA
- NGOs advocate wide scope in TSCA risk evaluations
- NGOs focus on 'conditions of use' in TSCA framework rules suit

Further Information:

- EPA release
- Problem formulations
- Systematic review approach
- Asbestos Snur (pre-publication)

Regulators need industry data on PA oligomers, Germany says

Substances are found in plastic kitchen utensils

5 June 2018 / Food & drink, Food contact, Germany, Risk assessment

Germany's Federal Institute for Risk Assessment (BfR) has called on industry to provide more toxicology information on polyamide (PA) oligomers in plastic kitchen utensils.

The institute has published its risk assessment of two selected PA oligomers, PA6 and PA66. However, it was unable to give a definitive answer on the safety of kitchen utensils containing them because of the lack of relevant data.

The assessment team established a tolerable personal exposure level of 90micrograms/day. This is based on the "threshold of toxicological concern" approach and categorisation of the substances by chemical structure. Health effects are unlikely below this exposure level, the report says.

But the exposure estimates suggested that real exposures are likely to exceed this level, reaching up to 17.6 milligrams/day.

Thus, toxicology data from industry is required to confirm the safety of the substances in kitchen utensils at these higher exposures, the BfR concludes.

Oligomers are polymer fragments: they comprise the same repeating chemical structures as polymers, but are limited to only a few monomers. PA oligomers form in kitchen utensils during polymerisation, and because of their relatively small size, they can migrate into food on contact.

The substances are type III substances according to chemical structure, under the Cramer classification system. This means the structures "permit no strong initial impression of safety and may even suggest a significant toxicity". But they are not suspected of being carcinogenic or genotoxic, the report says.

Further Information:

- Report

Echa to probe 'abandoned' REACH lead dossiers

Clean up of joint submissions list planned after summer

5 June 2018 / Europe, REACH, Substance registration

Echa is to look into lead dossiers in its REACH joint submissions list that it says "will probably be abandoned".

The list still contains a large number of missing lead dossiers for substances logged several years ago under past deadlines, following the final REACH registration deadline of 31 May.

As of 1 June it showed that 16,008 joint registrations have been made so far under the 2010, 2013 and 2018 deadlines, but 855 lead dossiers are still missing.

In a joint submission, the lead registrant first enters an intention to register a substance. They are then expected to submit a lead dossier on behalf of the consortium of manufacturers. The lead dossier is checked for completeness and once the fees are paid, the substance is formally registered.

Echa says it expects a significant portion of the 855 dossiers to be submitted at some point, while others – most of them dating back to the 2010 and 2013 deadlines – are unlikely to come in.

This happens when a substance information exchange forum (Sief) has been created, Echa says, but the lead registrant has subsequently changed the substance identity and created another joint submission, or companies have lowered the production volumes or ceased production altogether.

Echa says that in June 2016 it removed some of the "empty" joint registrations when it introduced the current version of the REACH-IT registration platform. But it left those that showed signs of activity in the system to allow more time for submissions.

The agency does not say how many of the missing lead dossiers from before June 2016, were eventually submitted, but according to Chemical Watch calculations, there are currently 78 entries from that period still with no lead documents. Echa says these are most likely to have been abandoned, since the registration "did not materialise".

The final tally, including those from more recent registrations, is likely to exceed 78 as more of the 855 currently missing lead dossiers may turn out to be "abandoned". Echa, however, does not have an estimate on the final number.

It says the number is rapidly falling: in the middle of May there were more than 2,000 joint submissions without a lead dossier.

Final deadline focus

Echa says it intends to clean up the joint submissions list by contacting lead registrants and asking them if they still plan to register.

However, it will wait for dossier checks for 2018 registrations to be completed. This is likely to take until September.

The number of missing dossiers is likely to change daily until then, but for now Echa says it has no plans to remove them from the list, even if they are considered "abandoned".

"At the moment the focus is on helping those companies who proactively contact us with registration intentions," said the spokesperson.

Meanwhile, "should someone else – for example a downstream user – want to register the substance and be blocked by this empty joint submission, we will remove it to enable registration if the original lead registrant will not register," they added.

By the 31 May deadline, Echa received 33,363 registration dossiers for 11,114 substances manufactured or imported in quantities of between one and 100 tonnes/year.

For all three registration deadlines combined, the agency has received 88,319 dossiers for 21,551 chemicals.

The numbers were significantly short of initial estimates and SMEs trade body Ueapme has questioned why "thousands" of expected substance registrations did not appear.

Clelia Oziel

Reporter

Related Articles

- More than 21,000 substances registered under REACH
- No convincing answers on 'missing' REACH 2018 substances – Ueapme

Further Information:

- Echa list

OTHER ARTICLES

Americans are Filled With Toxic Chemicals From Cosmetics, Congress May Finally Take Action ...

Good News Network

Currently, cosmetic manufacturers have no legal obligation in the U.S. to report health problems from their **products**, many of which contain known ...

Lowe's commits to phasing out toxic paint removal products

Salisbury Post

"We care deeply about the health **and** safety of our customers, **and** great ... **and** suppliers to market new alternatives **and** lead change in the industry.

The missing science: Could our addiction to plastic be poisoning us?

UN Environment (press release)

When scientists took a proper look at these **substances**, they found them to be ... Until recently, much of the research, **and** concern, focused on food ...

EPA Response to Public Comments Related to the Supplemental Files Supporting the TSCA Scope Documents for the First Ten Risk Evaluations

May 2018

Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, DC

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This document provides the responses of the U.S. Environmental Protection Agency (EPA)/Office of Pollution Prevention and Toxics (OPPT) to the public comments on the supplemental files supporting the scope documents for the risk evaluations of the first ten chemicals that EPA is conducting under the amended Toxic Substances Control Act (TSCA). These supplemental documents discussed the initial systematic review activities for the TSCA risk evaluations, specifically the data gathering and literature screening strategy.

The *Strategy for Conducting Literature Searches* describes the initial methods, approaches and procedures that EPA used for identifying, compiling and screening publicly available information to support the development of the TSCA risk evaluations. The *Bibliography* documents for each TSCA scope document provide the bibliographic citations that were identified from the initial literature search and included based on the title and abstract screening.

EPA released the documents to the public on June 22, 2017. EPA opened the dockets on June 19, 2017 to receive information from the public. The public comment period ended on September 19, 2017.

Table 1 lists the chemical substances under evaluation, docket number information and web links where the *Strategy for Conducting Literature Searches* and *Bibliography* documents can be found along with the associated TSCA Scope documents and public comments. Table 2 summarizes the public comments that EPA received for the supplemental files.

Table 1. Docket and Web Link Information for the TSCA Scope Documents and Associated Supplemental Files

Chemical Name	CASRN	Docket Number	Web link to TSCA Scope, Literature Search Strategy and Bibliography Documents
Asbestos	1332-21-4	EPA-HQ-OPPT-2016-0736	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/asbestos-scope-document-and-supplemental-files"]
1-Bromopropane (1-BP)	106-94-5	EPA-HQ-OPPT-2016-0741	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/1-bromopropane-1-bp-scope-document-and-supplemental"]
Carbon Tetrachloride (CCl_4)	56-23-5	EPA-HQ-OPPT-2016-0733	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/carbon-tetrachloride-scope-document-and-supplemental"]
1,4-Dioxane	123-91-1	EPA-HQ-OPPT-2016-0723	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/14-dioxane-scope-

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			document-and-supplemental-files"]
Cyclic Aliphatic Bromide Cluster (HBCD)	25637-99-4; 3194-55-6; and 3194-57-8	EPA-HQ-OPPT-2016-0735	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/cyclic-aliphatic-bromides-cluster-hbcd-cluster-scope"]
Methylene Chloride	75-09-2	EPA-HQ-OPPT-2016-0742	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/methylene-chloride-scope-document-and-supplemental-files"]
N-Methylpyrolidone (NMP)	872-50-4	EPA-HQ-OPPT-2016-0743	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/n-methylpyrrolidone-nmp-scope-document-and-supplemental"]
Perchloroethylene (PERC)	127-18-4	EPA-HQ-OPPT-2016-0732	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/perchloroethylene-scope-document-and-supplemental-files"]
Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone; PV29)	81-33-4	EPA-HQ-OPPT-2016-0725	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/pigment-violet-29-anthra219-def6510-defdiisoquinoline"]
Trichloroethylene (TCE)	79-01-6	EPA-HQ-OPPT-2016-0737	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/trichloroethylene-tce-scope-document-and-supplemental"]

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Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
1	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should consider other tools for systematic review: EPA has also proposed to extract data results in the DRAGON software. We strongly encourage EPA to also consider other potential software tools that have been developed and actively incorporated into the process of systematic review, such as Swift Reviewer, Active Screener, HAWC (Health Assessment Workplace Collaborative).	*Response for comments #1-3* EPA/OPPT is considering the use of various tools and/or approaches to support the various stages of the systematic review process of TSCA risk evaluations. DRAGON and DistillerSR are examples of tools that EPA/OPPT uses for the systematic review of TSCA risk
2	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should incorporate appropriate tools for updating and evaluating systematic reviews in their chemical assessments. EPA should evaluate the Cochrane Collaboration panel's tool for updating guidance for systematic reviews, published guidance in 2016 for determining when it is appropriate to update a systematic review and outlining the steps for performing the update to assess the applicability of environmental chemicals given that Cochrane systematic reviews. It will be critical for EPA to develop tools to assist with the process of evaluating existing systematic reviews, particularly as this field continues to rapidly expand and more systematic reviews relevant to environmental health questions are published in the scientific literature, potentially of variable quality. One tool which might be helpful for evaluating the risk of bias in systematic reviews is the ROBIS tool, which the NAS committee utilized in their report. Another tool which may be helpful in this process is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), used by authors of systematic reviews to improve the reporting of elements relevant to the systematic review and meta-analyses. We also strongly recommend EPA identify tools that may potentially not be appropriate for human health chemical assessments without modification, such as those developed in other fields, such as clinical or preclinical animal or human studies.	
3	[HYPERLINK	TCE Section 5.3.1, p.15: While EPA has limited its data to that which is publically	

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
	"https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	available, it appears that the software being used by those who will screen the data is proprietary, i.e., IFC's DRAGON. It is not clear whether the public will be able to access this database and/or see how the software instructs, encourages, or limits the options for the reviewer. We suggest that EPA provide snap-shots of pages used by the reviewers, as well as the results of the analyses.	evaluations. EPA/OPPT is considering the adoption of the OECD Harmonized Templates (OHTs) for extracting various data streams. EPA/OPPT is exploring to use DistillerSR as the tool for data extraction. EPA/OPPT will rely on HERO as the "warehouse" for all citations included in the TSCA risk

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
			evaluations. Each chemical assessment has a "project page" that will be made public when EPA publishes the draft risk evaluations. EPA/OPPT is committed to transparency and will provide documentation of how the systematic review has been conducted to support the TSCA

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
			risk evaluations.
4	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0735-0058"]	We request that EPA provide (1) a clear definition of "off topic" and "on-topic" and (2) a general scope of how "off topic" and "on-topic" studies are anticipated to be utilized in the evaluation. For example, are "off topic" studies only identified and utilized as supporting information to confirm [or reject] information found in "on-topic" studies?	EPA/OPPT included definitions of on-topic and off-topic references on page 2 of each *Bibliography* document that accompanied each TSCA Scope document. Also the definition was included in section 1.3 of each TSCA Scope document. The definitions have also been

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	**Commenter**	**Comment Summary**	**EPA's Response**
			included in section 3.2.2.1.1 of document entitled *Application of Systematic Review in TSCA Risk Evaluations*.
5	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should provide exclusion reasons for off topic citations.	*Response for comments #5-6*
6	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should stratify its exclusion criteria separately at the title and abstract and full text screening steps.	The *Strategy for Conducting Literature Searches* documents provided the inclusion

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
			and exclusion criteria used for the title/abstract screening. References that did not meet the inclusion criteria were excluded and considered *off-topic*. The inclusion and exclusion criteria for full text screening are included in each of the TSCA Problem Formulation documents for the first

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
			ten chemical assessments .
7	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should not exclude studies based on language.	EPA/OPPT will translate studies on a case-by - case basis.
8	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should have two independent reviewers for screening steps.	*Response for comments #8-11* EPA/OPPT pilots the screening criteria to ensure a level of proficiency of each screener in each subject matter area. Additionally, each article is generally screened by two different
9	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should clearly document decisions related to the identification and search. Particularly, the number of studies that are reviewed by a senior-level technician and the feedback and guidance provided to individual screeners.	
10	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should clarify how it will handle discrepancies in the inclusion/exclusion and tagging process and use a third party reviewer as an arbiter for decisions when consensus is not reached.	
11	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should clearly outline the process for handling anticipated overlap with literature relevant to multiple topics. EPA should describe whether the same reviewer will be responsible for screening papers with inclusion/exclusion criteria across multiple topics or whether different reviewers are responsible only for screening studies for one particular topic.	

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
			reviewers. All of the screening decisions are being documented. Refer to the *Strategy for Conducting Literature Searches* documents and section 3.2.2.1 of document entitled *Application of Systematic Review in TSCA Risk Evaluations* for more information on the title/abstract screening.

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
12	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should explicitly include stopping rules in the form of deadlines or criteria for when the body of included relevant studies will be finalized for the purposes of the chemicals assessment.	The body of information compiled in the *Bibliography* documents for each TSCA scope document will be the primary pool of studies that will be considered in the TSCA risk evaluations along information submitted during public comment periods prior to the publication of the draft TSCA risk evaluations.

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
			Targeted supplemental searches may be conducted to address specific needs for the analysis phase (e.g., to located specific data for building exposure scenarios and modeling).
13	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should ensure gray literature search results are adequately screened. EPA's gray literature search strategy proposes to utilize Google's API to develop custom searches and return the first 100 results, sorted by predicted relevancy so that the results likely to be most relevant are screened first. We recommend that EPA ensure that an adequate number of search results are screened. EPA should consider "snowball searching," where the citations of included (i.e., on-topic) references are searched as well as using databases such as Web of Science to search for references that cite the included citations.	EPA/OPPT will include backward searching (also called snowball searching) in future searches. EPA/OPPT may refine

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
			the search strategy for future assessments to ensure that relevant gray literature is captured.
14	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	TCE Section 4.4, p.14: With regard to the exclusion criterion, "Links that were broken at the time of the search", an additional search step may find them before exclusion. We suggest that a search engine such as Google be used to see if title of the document is sufficient to obtain a working URL.	Two types of broken links were identified when searching for gray literature: (1) those associated with entire sites that were "down" or inactive and (2) links on active sites that were no longer

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
			appropriate. In the event of the latter, particularly for links on EPA's website, which has recently undergone a large-scale reorganization, the title of documents will be searched via Google to determine if the document is available at another location.
15	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	TCE Section 4.4, p.14: In the exclusion criterion for peer-reviewed articles, "peer reviewed literature was assumed to be captured in searches of the databases of peer-reviewed literature." If the databases of peer-reviewed literature are based on journals, books, and government reports, the conclusion in the criterion may not be valid. For TCE for example, Toxicology Excellence for Risk Assessment	Peer reviewed literature that was captured

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
		(TERA, now part of the University of Cincinnati) had an externally peer reviewed analysis of EPA's RfC that was publically available months before it was published in a journal. This may also be true for many analyses and reviews performed in State regulatory agencies that, unlike academia, do not include journal publications in their criteria for professional advancement.	during the search of the gray literature was excluded only if it was clearly shown to be available in the peer-reviewed literature, for example, with a journal citation and/or DOI. The peer reviewed analysis by TERA referenced in the comment would not be excluded from the results of

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
			the gray literature search. The TERA reference will be added to the on-topic pool of references supporting the TSCA risk evaluation for trichloroethylene.
16	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should rely on existing IRIS assessments for hazard identification. Moving forward, EPA should complete hazard identification or add additional studies only through a systematic review process, which integrates animal, human and mechanistic evidence as recommended by the recent NAS report. For the scoping document, EPA should include all hazards identified in the literature, and not make decisions about their relevance to the risk evaluation until a systematic review has been completed. EPA should develop criteria to evaluate the internal validity (risk of bias) of individual studies, utilizing existing tools that have been developed and empirically demonstrated on environmental health studies such as the Navigation	*Response for comments #16-18* EPA/OPPT will use previous assessments such as the IRIS assessments

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
		Guide or the Office of Health Assessment and Translation (OHAT approach). We also recommend that EPA not using a scoring system to evaluate study quality. Data generated by alternative test methods (such as high-throughput screening methods) are not different than any other type of in vitro or cell-based assay data that would be considered in a systematic review. These data can be used to support conclusions, but hazard classification should never be made based on high-throughput or other kinds of mechanistic data alone.	as a starting point for identifying key and supporting studies to inform the human health hazard assessment, including dose-response analysis. The relevant studies will be evaluated using the data/information quality criteria in the document entitled *Application of Systematic*
17	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0061"]	Use of existing IRIS assessments: To assist the Agency in meetings its deadlines for risk evaluations, previous findings on hazard and risk from the IRIS assessments should be presumed valid and incorporated in risk evaluations. Moving forward, EPA should complete hazard identification or add additional studies through a systematic review process, which integrates animal, human and mechanistic evidence as recommended by the recent NAS report on Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Disrupting Chemicals [ADDIN EN.CITE <EndNote><Cite><Author>National Academy of Sciences</Author><Year>2017</Year><RecNum>35</RecNum><IDText>3982546</IDText><DisplayText>(National Academy of Sciences, 2017)</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="wfedfw0vlx9tdjedfrmpp5e52sfrwe555ptt" timestamp="1511286716">35</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>National Academy of Sciences,</author></authors></contributors><titles><title>Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active	

Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
#	Commenter	Comment Summary	EPA's Response
		chemicals</title></titles><pages>180</pages><dates><year>2017</year></dates><pub-location>Washington, D.C.</pub-location><publisher>The National Academies Press</publisher><label>3982546</label><urls><related-urls><url>http://dx.doi.org/10.17226/24758</url></related-urls></urls><electronic-resource-num>10.17226/24758</electronic-resource-num><language>English</language></record></Cite></EndNote>].	*Review in TSCA Risk Evaluations.* Refer to each of the TSCA Problem Formulation documents for details on how the PECOs are considering the information of the IRIS assessments for setting inclusion criteria for the full text screening. Regarding negative studies, the weight of evidence analysis is
18	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	TCE Section 3.3.1, p.9-10: The intent appears to be to use the IRIS 2011 evaluation without independent review of the literature, and to start the literature search at January 2010. However, [HYPERLINK "file:///C:\\Users\\Iris%20Camacho\\Desktop\\TSCA%20SR%20protocol_v9_121617_clean_beck_template.docx" \l "_ENREF_27" \o "U.S. EPA, 2011 #65"] discounts the negative rat studies as "not entirely adequate", even including the NTP 1988 study which was designed to overcome the high mortality in the NCI 1976 and NTP 1990 rat studies that had high mortality (using the same rat strain) by using five different strains of rat. While one was the same as the two previous, presumably as a control, that was not the case for all of the rat strains. Similarly, [HYPERLINK "file:///C:\\Users\\Iris%20Camacho\\Desktop\\TSCA%20SR%20protocol_v9_121617_clean_beck_template.docx" \l "_ENREF_27" \o "U.S. EPA, 2011 #65"] states "Weaknesses in the evidence include lack of a clear dose-related response in the incidence of cardiac defects, and the broad variety of cardiac defects observed, such that they cannot all be grouped easily by type or reported inhalation studies being negative for developmental toxicity, EPA's document uses the positive results in oral studies to calculate the RfC. We suggest that, at a minimum, TSCA independently review the data in the negative studies discounted by the IRIS document, as well as any recent publication. These example cited in the full comment demonstrate the discounting credible negative results in favor of positive studies regardless of route of exposure. Use of PBPK modeling is not justified for route-of-exposure extrapolation when data exist for that route of exposure.	

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			an integrative and interpretive process that considers both data/information in favor (e.g., positive study) or against (e.g., negative study) a given hypothesis within the context of the assessment question(s) being evaluated in the risk evaluation.

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API=Application Programming Interface	OHAT=The NTP Office of Health Assessment and Translation
DOD=United States Department of Defense	OECD=Organisation for Economic Co-operation and Development
DOI=Digital Object Identifier	OPPT=The Environmental Protection Agency Office of Pollution Prevention and Toxics
DRAGON=	PBPK=Physiologically-based pharmacokinetic
EPA=Environmental Protection Agency	PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses
EPA/OPPT=Environmental Protection Agency Office of Pollution Prevention and Toxics	ROBIS=tool for assessing Risk of Bias in systematic reviews
HERO=Health and Environmental Research Online	TERA=Toxicology Excellence for Risk Assessment
IRIS=Integrated Risk Information System	TCE=Trichloroethylene
NAS=National Academy of Sciences	TSCA=Toxic Substances Control Act
NRDC=National Resources Defense Council	

EPA Response to Public Comments Related to the Supplemental Files Supporting the TSCA Scope Documents for the First Ten Risk Evaluations

May 2018

Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, DC

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This document provides the responses of the U.S. Environmental Protection Agency (EPA)/Office of Pollution Prevention and Toxics (OPPT) to the public comments on the supplemental files supporting the scope documents for the risk evaluations of the first ten chemicals that EPA is conducting under the amended Toxic Substances Control Act (TSCA). These supplemental documents discussed the initial systematic review activities for the TSCA risk evaluations, specifically the data gathering and literature screening strategy.

The *Strategy for Conducting Literature Searches* describes the initial methods, approaches and procedures that EPA used for identifying, compiling and screening publicly available information to support the development of the TSCA risk evaluations. The *Bibliography* documents for each TSCA scope document provide the bibliographic citations that were identified from the initial literature search and included based on the title and abstract screening.

EPA released the documents to the public on June 22, 2017. EPA opened the dockets on June 19, 2017 to receive information from the public. The public comment period ended on September 19, 2017.

Table 1 lists the chemical substances under evaluation, docket number information and web links where the *Strategy for Conducting Literature Searches* and *Bibliography* documents can be found along with the associated TSCA Scope documents and public comments. Table 2 summarizes the public comments that EPA received for the supplemental files.

Table 1. Docket and Web Link Information for the TSCA Scope Documents and Associated Supplemental Files

Chemical Name	CASRN	Docket Number	Web link to TSCA Scope, Literature Search Strategy and Bibliography Documents
Asbestos	1332-21-4	EPA-HQ-OPPT-2016-0736	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/asbestos-scope-document-and-supplemental-files"]
1-Bromopropane (1-BP)	106-94-5	EPA-HQ-OPPT-2016-0741	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/1-bromopropane-1-bp-scope-document-and-supplemental"]
Carbon Tetrachloride (CCl_4)	56-23-5	EPA-HQ-OPPT-2016-0733	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/carbon-tetrachloride-scope-document-and-supplemental"]
1,4-Dioxane	123-91-1	EPA-HQ-OPPT-2016-0723	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/14-dioxane-scope-

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			document-and-supplemental-files"]
Cyclic Aliphatic Bromide Cluster (HBCD)	25637-99-4; 3194-55-6; and 3194-57-8	EPA-HQ-OPPT-2016-0735	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/cyclic-aliphatic-bromides-cluster-hbcd-cluster-scope"]
Methylene Chloride	75-09-2	EPA-HQ-OPPT-2016-0742	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/methylene-chloride-scope-document-and-supplemental-files"]
N-Methylpyrolidone (NMP)	872-50-4	EPA-HQ-OPPT-2016-0743	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/n-methylpyrrolidone-nmp-scope-document-and-supplemental"]
Perchloroethylene (PERC)	127-18-4	EPA-HQ-OPPT-2016-0732	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/perchloroethylene-scope-document-and-supplemental-files"]
Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone; PV29)	81-33-4	EPA-HQ-OPPT-2016-0725	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/pigment-violet-29-anthra219-def6510-defdiisoquinoline"]
Trichloroethylene (TCE)	79-01-6	EPA-HQ-OPPT-2016-0737	[HYPERLINK "https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/trichloroethylene-tce-scope-document-and-supplemental"]

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Table 2. Summary of Public Comments and EPA Responses Related to the Supplemental Files Associated with the TSCA Scope Documents for the First Ten Risk Evaluations			
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1	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should consider other tools for systematic review: EPA has also proposed to extract data results in the DRAGON software. We strongly encourage EPA to also consider other potential software tools that have been developed and actively incorporated into the process of systematic review, such as Swift Reviewer, Active Screener, HAWC (Health Assessment Workplace Collaborative).	*Response for comments #1-3* EPA/OPPT is considering the use of various tools and/or approaches to support the various stages of the systematic review process of TSCA risk evaluations. DRAGON and DistillerSR are examples of tools that EPA/OPPT uses for the systematic review of TSCA risk
2	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should incorporate appropriate tools for updating and evaluating systematic reviews in their chemical assessments. EPA should evaluate the Cochrane Collaboration panel's tool for updating guidance for systematic reviews, published guidance in 2016 for determining when it is appropriate to update a systematic review and outlining the steps for performing the update to assess the applicability of environmental chemicals given that Cochrane systematic reviews. It will be critical for EPA to develop tools to assist with the process of evaluating existing systematic reviews, particularly as this field continues to rapidly expand and more systematic reviews relevant to environmental health questions are published in the scientific literature, potentially of variable quality. One tool which might be helpful for evaluating the risk of bias in systematic reviews is the ROBIS tool, which the NAS committee utilized in their report. Another tool which may be helpful in this process is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), used by authors of systematic reviews to improve the reporting of elements relevant to the systematic review and meta-analyses. We also strongly recommend EPA identify tools that may potentially not be appropriate for human health chemical assessments without modification, such as those developed in other fields, such as clinical or preclinical animal or human studies.	
3	[HYPERLINK	TCE Section 5.3.1, p.15: While EPA has limited its data to that which is publically	

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	"https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	available, it appears that the software being used by those who will screen the data is proprietary, i.e., IFC's DRAGON. It is not clear whether the public will be able to access this database and/or see how the software instructs, encourages, or limits the options for the reviewer. We suggest that EPA provide snap-shots of pages used by the reviewers, as well as the results of the analyses.	evaluations. EPA/OPPT is considering the adoption of the OECD Harmonized Templates (OHTs) for extracting various data streams. EPA/OPPT is exploring to use DistillerSR as the tool for data extraction. EPA/OPPT will rely on HERO as the "warehouse" for all citations included in the TSCA risk

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			evaluations. Each chemical assessment has a "project page" that will be made public when EPA publishes the draft risk evaluations. EPA/OPPT is committed to transparency and will provide documentation of how the systematic review has been conducted to support the TSCA

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			risk evaluations.
4	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0735-0058"]	We request that EPA provide (1) a clear definition of "off topic" and "on-topic" and (2) a general scope of how "off topic" and "on-topic" studies are anticipated to be utilized in the evaluation. For example, are "off topic" studies only identified and utilized as supporting information to confirm [or reject] information found in "on-topic" studies?	EPA/OPPT included definitions of on-topic and off-topic references on page 2 of each *Bibliography* document that accompanied each TSCA Scope document. Also the definition was included in section 1.3 of each TSCA Scope document. The definitions have also been

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#	Commenter	Comment Summary	EPA's Response
			included in section 3.2.2.1.1 of document entitled *Application of Systematic Review in TSCA Risk Evaluations*.
5	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should provide exclusion reasons for off topic citations.	*Response for comments #5-6*
6	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should stratify its exclusion criteria separately at the title and abstract and full text screening steps.	The *Strategy for Conducting Literature Searches* documents provided the inclusion

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			and exclusion criteria used for the title/abstract screening. References that did not meet the inclusion criteria were excluded and considered *off-topic*. The inclusion and exclusion criteria for full text screening are included in each of the TSCA Problem Formulation documents for the first

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			ten chemical assessments .
7	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should not exclude studies based on language.	EPA/OPPT will translate studies on a case-by - case basis.
8	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should have two independent reviewers for screening steps.	*Response for comments #8-11* EPA/OPPT pilots the screening criteria to ensure a level of proficiency of each screener in each subject matter area. Additionally, each article is generally screened by two different
9	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should clearly document decisions related to the identification and search. Particularly, the number of studies that are reviewed by a senior-level technician and the feedback and guidance provided to individual screeners.	
10	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should clarify how it will handle discrepancies in the inclusion/exclusion and tagging process and use a third party reviewer as an arbiter for decisions when consensus is not reached.	
11	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should clearly outline the process for handling anticipated overlap with literature relevant to multiple topics. EPA should describe whether the same reviewer will be responsible for screening papers with inclusion/exclusion criteria across multiple topics or whether different reviewers are responsible only for screening studies for one particular topic.	

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			reviewers. All of the screening decisions are being documented. Refer to the *Strategy for Conducting Literature Searches* documents and section 3.2.2.1 of document entitled *Application of Systematic Review in TSCA Risk Evaluations* for more information on the title/abstract screening.

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12	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should explicitly include stopping rules in the form of deadlines or criteria for when the body of included relevant studies will be finalized for the purposes of the chemicals assessment.	The body of information compiled in the *Bibliography* documents for each TSCA scope document will be the primary pool of studies that will be considered in the TSCA risk evaluations along with information submitted during public comment periods prior to the publication of the draft TSCA risk evaluations.

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			Targeted supplemental searches may be conducted to address specific needs for the analysis phase (e.g., to located specific data for building exposure scenarios and modeling).
13	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should ensure gray literature search results are adequately screened. EPA's gray literature search strategy proposes to utilize Google's API to develop custom searches and return the first 100 results, sorted by predicted relevancy so that the results likely to be most relevant are screened first. We recommend that EPA ensure that an adequate number of search results are screened. EPA should consider "snowball searching," where the citations of included (i.e., on-topic) references are searched as well as using databases such as Web of Science to search for references that cite the included citations.	EPA/OPPT will include backward searching (also called snowball searching) in future searches. EPA/OPPT may refine

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			the search strategy for future assessments to ensure that relevant gray literature is captured.
14	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	TCE Section 4.4, p.14: With regard to the exclusion criterion, "Links that were broken at the time of the search", an additional search step may find them before exclusion. We suggest that a search engine such as Google be used to see if title of the document is sufficient to obtain a working URL.	Two types of broken links were identified when searching for gray literature: (1) those associated with entire sites that were "down" or inactive and (2) links on active sites that were no longer

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			appropriate. In the event of the latter, particularly for links on EPA's website, which has recently undergone a large-scale reorganization, the title of documents will be searched via Google to determine if the document is available at another location.
15	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0062"]	TCE Section 4.4, p.14: In the exclusion criterion for peer-reviewed articles, "peer reviewed literature was assumed to be captured in searches of the databases of peer-reviewed literature." If the databases of peer-reviewed literature are based on journals, books, and government reports, the conclusion in the criterion may not be valid. For TCE for example, Toxicology Excellence for Risk Assessment	Peer reviewed literature that was captured

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		(TERA, now part of the University of Cincinnati) had an externally peer reviewed analysis of EPA's RfC that was publically available months before it was published in a journal. This may also be true for many analyses and reviews performed in State regulatory agencies that, unlike academia, do not include journal publications in their criteria for professional advancement.	during the search of the gray literature was excluded only if it was clearly shown to be available in the peer-reviewed literature, for example, with a journal citation and/or DOI. The peer reviewed analysis by TERA referenced in the comment would not be excluded from the results of

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			the gray literature search. The TERA reference will be added to the on-topic pool of references supporting the TSCA risk evaluation for trichloroethylene.
16	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0055"]	EPA should rely on existing IRIS assessments for hazard identification. Moving forward, EPA should complete hazard identification or add additional studies only through a systematic review process, which integrates animal, human and mechanistic evidence as recommended by the recent NAS report. For the scoping document, EPA should include all hazards identified in the literature, and not make decisions about their relevance to the risk evaluation until a systematic review has been completed. EPA should develop criteria to evaluate the internal validity (risk of bias) of individual studies, utilizing existing tools that have been developed and empirically demonstrated on environmental health studies such as the Navigation	*Response for comments #16-18* EPA/OPPT will use previous assessments such as the IRIS assessments

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		Guide or the Office of Health Assessment and Translation (OHAT approach). We also recommend that EPA not using a scoring system to evaluate study quality. Data generated by alternative test methods (such as high-throughput screening methods) are not different than any other type of in vitro or cell-based assay data that would be considered in a systematic review. These data can be used to support conclusions, but hazard classification should never be made based on high-throughput or other kinds of mechanistic data alone.	as a starting point for identifying key and supporting studies to inform the human health hazard assessment, including dose-response analysis. The relevant studies will be evaluated using the data/information quality criteria in the document entitled *Application of Systematic*
17	[HYPERLINK "https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0061"]	Use of existing IRIS assessments: To assist the Agency in meetings its deadlines for risk evaluations, previous findings on hazard and risk from the IRIS assessments should be presumed valid and incorporated in risk evaluations. Moving forward, EPA should complete hazard identification or add additional studies through a systematic review process, which integrates animal, human and mechanistic evidence as recommended by the recent NAS report on Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Disrupting Chemicals [ADDIN EN.CITE <EndNote><Cite><Author>National Academy of Sciences</Author><Year>2017</Year><RecNum>35</RecNum><IDText>3982546</IDText><DisplayText>(National Academy of Sciences, 2017)</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="wfedfw0vlx9tdjedfrmpp5e52sfrwe555ptt" timestamp="1511286716">35</key></foreign-keys><ref-type name="Book">6</ref-type><contributors><authors><author>National Academy of Sciences,</author></authors></contributors><titles><title>Application of systematic review methods in an overall strategy for evaluating low-dose toxicity from endocrine active	

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